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PREFRONTAL ULTRASONIC IRRADIATION—A SUBSTITUTE FOR LOBOTOMY

P. A. LINDSTROM, M.D.
PITTSBURGH

THE AIM of this investigation was to find a way of producing the desirable effects of a prefrontal lobotomy with minimal and reasonably well-controlled damage to the brain substance. Most of the serious and unpredictable complications following lobotomies are due either to excessive and misplaced sectioning * or to the hemorrhage, necrosis, and degeneration occurring in proximity to the operative site.† It appeared essential, therefore, to avoid actual cutting of the frontal lobes and to eliminate extensive trauma caused by the aspiration needle and the thermocautery. Theoretically, it seemed possible to achieve this result with ultrasound. Because of insufficient data regarding the effects of high frequency, high intensity sound on brain tissue, this problem was first studied in experimental animals. The results, some of which will be reported here, seemed to justify a clinical trial, and a technique was developed for irradiation of the human prefrontal lobes with ultrasound as a possible substitute for lobotomy.

The subject of selected sectioning of the prefrontal lobes has been reviewed by several writers.‡ There is general agreement that when the tissue destruction is limited to small areas of the frontal lobes, complications decrease both in severity and in frequency. However, it remains an open question as to what extent different clinical conditions can be more satisfactorily controlled by placing the tissue destruction in specific locations within the prefrontal lobes. For further details of the history of psychosurgery from the time of Burckhardt [22] (1891) and Egas Moniz [23] (1936), reference is made to several authors.§

PREVIOUS INVESTIGATIONS OF EFFECT OF ULTRASOUND ON BRAIN TISSUE

In 1927, Wood and Loomis [26] published their experiments on the biological effect of high frequency sound waves of great intensity. Similar studies were done in 1928 by Harvey and Loomis [27] and Schmitt, Olson, and Johnson,[28] followed by the investigations of other authors. During the last 15 years an extensive literature has grown around the use of ultrasound in physical medicine at intensities that do

Presented at the meeting of the Scandinavian Neurosurgical Society August, 1953, in Helsinki, Finland.

The experimental studies are from the Addison H. Gibson Laboratory, University of Pittsburgh. The clinical investigation is from the Surgical Service, Veterans Administration Hospital, Pittsburgh, and the Department of Surgery, University of Pittsburgh School of Medicine.

* References 1 to 5.

† References 2, and 6 to 9.

‡ References 10 to 21.

§ References 1, 11, 13, 14, 24, and 25.

not cause histological alterations in the exposed tissue. The indications and the results are somewhat comparable to those of diathermy. The method of application of ultrasound in physical therapy suggests that, in part, it is a local thermal effect which brings symptomatic relief to painful joints and muscles.

Four years ago, when this study was first planned, few experiments had been made to determine the effect of ultrasound on the animal brain. Lynn and associates‖ described, in 1942, how they had obtained various neurological symptoms in dogs "in association with corresponding gross and microscopic brain lesions" by transcranial application of focused ultrasound with a frequency of 835 kc. per second. "Unfortunately there was always a necrosis of the scalp where the apparatus was applied." In 1944, Lynn and Putnam,[31] using essentially the same technique in more detailed experiments, caused a minor tissue reaction or an area of shallow necrosis on the surface of animal brains; at the margin of the necrosis they found that the ganglion cells were more damaged than the glial elements, and the blood vessels were the least affected. Allegranza [32] (1950), applying 4 to 6 watts per square centimeter and a frequency of 800 to 1,000 kc. per second, caused such necrosis to the scalp, skull, and brain of guinea pigs that he concluded that any use of ultrasound for therapeutic purposes on human beings was not feasible with the technique he had employed. Gregg [33] (1944), Leonhardt [34] (1949), Manns¶ (1951), Heyck and Höpker [35] (1952), and Peters [36] (1952), in similar experiments, produced tissue damage to the meninges, to the cortex, and to some extent to the subcortical region by transcranial irradiation of rats and other small animals. Apart from the sloughing of the scalp, the cell destruction in these experiments occurred mainly on the surface layers of the brain in the form of a shallow cup, with comparatively little involvement of the subcortex.

Wall and associates [37] wrote, in 1953, that it was the extensive necrosis of the brain surface found in earlier experiments which had discouraged further investigation, and they irradiated brains of cats and monkeys, through a skull opening, with focused ultrasound. A beam which may have an average intensity of 10 watts per square centimeter or less as it leaves the generating crystal can, by focusing, reach intensities of several hundred watts per square centimeter in certain small cross sections of the beams. Zubiani [38] (1951) stated that he avoided the skin necrosis in dogs by moving the sound head over the scalp and that he extended the lesions to deeper layers with crossed beams, but, unfortunately, his description was vague and no histological material was included. He mentioned that he had applied ultrasound of 500 kc. per second and 0.6 to 1.5 watts per square centimeter to the heads of patients with various brain disorders, but after 30 days of repeated treatments there were "no objective neurological signs noted" and "subjective symptoms," not further explained, "rapidly disappeared." Denier,[39] in 1948, gave an incomplete report of a series of three patients in whom he had aimed ultrasound (probably of an intensity used in physical therapy) in the direction of the diencephalon (!); his three patients suffered from dementia paralytica, torticollis, and Parkinsonism, respectively, and he seemed to have noticed some improvement in all of them. On the other hand, Heyck [40] showed that when ultrasound of the type commonly used in physical therapy was applied to the head, it had no therapeutic effect at all on a large number

‖ References 29 and 30.

¶ Manns, T., cited by Peters.[36]

of various brain diseases included in his investigation; nor did he notice any other reaction in the patients. Ballantine and associates [41] found no electroencephalographic abnormalities from a transcranial irradiation of human beings with peak intensities of 5 watts per square centimeter.

In accordance with Langevin's [42] principle (1917) for localization of submarines by sound, Dussik,# Ballantine,[43] French,[46] Hueter,[47] and their associates have made echograms or ultrasonograms of the human brain for the purpose of localizing its lateral ventricles. Their investigations show that ultrasound of low intensity (0.5 to 2 watts per square centimeter) can penetrate the human head from side to side without causing symptoms or, presumably, any histological changes, even to the skin. The practical value of this method of demonstrating the ventricles and such tumors as have a different density than the surrounding brain tissue is not yet established.

The mechanism responsible for the biological changes taking place in living tissue exposed to ultrasound has been the subject of much discussion, without being clearly defined. Some say that the mechanical forces of ultrasound play the major role.* Others maintain that the histological changes are caused to a great extent by heat generated by high frequency sound.† A number of other explanations have been given—for example, the depolymerization of macromolecules; the inactivation of enzymes, toxins, and protein hormones; the activation of oxidation reactions; the dispersion of solids in gels, and the ionization and formation of H_2O_2 in water; ovalbumin denatured by ultrasound behaves differently than heat-denatured ovalbumin.‡

The spinal cord of small animals has also been exposed to ultrasonic impulses through its overlying tissues,§ but the experimental conditions have been different from those of transcranial irradiation of the brain. The architecture of the cord is not the same as that of the brain, especially with respect to the arrangement of vessels and of gray substance. A part of the sound beam may reach the cord without necessarily having to penetrate bone, passing instead through interlaminar and interspinous openings. In transcranial irradiation, a layer of bone of varying thickness and structure interferes with the effect on the brain itself. It is, nevertheless, of interest that the larger cells of the cord, especially the anterior horn cells, have undergone more histological changes than the glial cells and the vessels following exposure to intense supersonic vibrations, an observation first made by Lynn and Putnam.[31]

EXPERIMENTAL STUDIES

The ultrasonic equipment ‖ employed in these experiments was the same in principle as that of the conventional types described, for example, by Carlin [67] and Pohlman.[68] It consisted mainly of a power supply, an oscillator, and an amplifier. In our apparatus the energy output of the amplifier was coupled to a quartz crystal by an induction coil located in the sound head itself. A small control crystal in the oscillator circuit governed the frequency of 1,000 kc. per second. The plane, circular crystal surface measured 1¼ in. (3.2 cm.) in diameter. The chamber which

References 44, and 45.

* References 26, 28, 37, and 48 to 53.

† References 54 to 56.

‡ References 33, 45, and 57 to 62.

§ References 31, 37, and 63 to 66.

‖ The ultrasonic generators used here were made by Mr. F. Nicsemann, in collaboration with Mr. S. Skallos.

carried the crystal was filled with oil, and the sound was transmitted from the quartz to an aluminum disk at the end of the sound head. The sound intensity averaged approximately 7 watts per square centimeter when the generator was set for maximum output. In limited parts of the beam, however, the intensity reached higher levels. Because of the well-known difficulties in measuring sound energy exactly, the sound intensities given in the following cases should not be taken as absolute figures but, rather, should be considered a means of demonstrating the comparative biological effects of increasing sound levels. An oscilloscope, allowing continuous observation of the pattern of the wave form, served as a monitor.

In preliminary experiments on living rabbits, the ultrasonic beam was directed to the brain through the overlying skin and bone. Usually the damage to the skin, meninges, and the surface of the cortex was severe compared with the minimal lesions in the subcortex. It was found that the skin necrosis could be avoided, at least within certain limits of sound intensity, by increasing the distance from the skin to the transducer and by rapid and constant exchange of the transmitting liquid. The cerebral cell changes, whether minor or in the form of necrosis, were concentrated along the dura and on the surface of the brain. The area of tissue damage extended into the brain in the shape of a shallow cup with its base toward the dura.

The initial animal studies demonstrated that it was difficult to standardize and predict the irradiation effect when the sound beam had first to penetrate the calvaria. In subsequent experiments on 10 dogs and 3 rabbits, the ultrasound was transmitted directly to the animal brain via a sterile liquid after a trephine opening had been made in the vault. The sound head was placed between 1.5 and 4 cm. from the brain surface. Saline, continuously exchanged, served as the transmitting medium. The plastic cup holding the fluid was cylindrical or cone-shaped. The circular open end, which was placed in direct contact with the dura or held against the bone around the trephine opening measured from 1.3 to 2 cm. in diameter. A watertight connection was obtained with the help of a soft rubber ring. Approximately the same area in all the brains was irradiated in these earlier experiments by directing the beam perpendicularly over the midportion of each hemisphere. The opening of the plastic cup containing the liquid medium was placed parasagittally so that its medial edge reached close to the midline of the brain. A few hemispheres were kept as controls. As the experiments progressed, the technique of application was changed; the size and shape of the plastic cup holding the transmitting fluid were altered, as was the radiation time; the frequency of 1,000 kc. per second remained constant. Some of the animals which had been irradiated as long as seven minutes with a moderately focused beam of destructive intensity were less active after exposure, and a few showed more or less severe paresis of one or more extremities. No convulsions or wound complications occurred. Most animals were killed after seven days by intravenous pentobarbital injection followed by exsanguination; two were kept three and four weeks, respectively. The brains were perfused in situ with 10% formalin through bilateral carotid injections and then removed and hardened in formalin or other fixative solutions.

ANATOMICAL FINDINGS

With direct ultrasonic irradiation of the animal brain through a surgical skull opening, the degree, extent, and depth of the tissue damage became a function of the intensity, exposure time, and size of the sound beam which reached the brain surface. The distance between the vibrating crystal and the brain and the mode of transmission of the sound were additional factors of importance. Greater uniformity in results was obtained by this technique on the 20 cerebral hemispheres than by transcranial irradiation. When the beam was aimed directly at the uncovered brain, the intensity of the damage tended to increase as compared with that received when a dural flap was turned, but the depth to which the cell changes were found was about the same in the two cases. An energy output of 0.5 to 2 watts per square centimeter was too low to produce histological brain lesions, even when the dura was opened. A sound beam averaging 5 to 7 watts per square centimeter and slightly focused constantly gave microscopic alterations within a rather circumscribed area within the path of the beam after three to five minutes of exposure. By a change in the

intensity and the length of exposure, the effects on the brain tissue, as observed later in the microscope, could deliberately be made to vary with a reasonable degree of accuracy, from a minimal damage of cells and myelin sheaths to necrosis of all tissue elements within a limited area. Minor cerebral damage was characterized by disruption of some fiber tracts, intracellular changes, and mild, spotty edema. The ganglion cells were evidently more sensitive than other cells. Disintegrated extravascular red cells were found here and there in proximity to normal-appearing vessel walls. With increased exposure, microscopic areas of necrosis were seen scattered diffusely in the brain substance, particularly in proximity to vessels. Generally there was only slight cellular reaction around such small foci of necrosis in the path of the sound, and the bulk of the tissue surrounding them retained its normal appearance. When the ultrasonic irradiation was pushed to even higher levels, the resulting grossly visible necrosis in the animal brain was illustrated by a yellowish or slightly hemorrhagic discoloration, usually limited to a small central part of the cross section along the beam axis. At that stage, not only fiber tracts and glial cells but also vessels underwent destruction, a common feature of which was liquefaction. The white matter showed gross lesions more readily than the cortex. In many instances there was a deep cone of total destruction in the white substance, while the overlying cortex presented only microscopic alterations.

After one to two minutes of exposure with approximately 5 to 7 watts per square centimeter, one sometimes found only a streak of yellowish-brown discoloration, about 1 to 2 mm. wide, along the boundary between the cortex and the white substance. Histologically, such a narrow band was composed of comparatively more damaged tissue. At times this subcortical discoloration was found to run parallel to the curving border line of a deep sulcus, while the top of the neighboring gyri, where the beam had entered, appeared normal.

To achieve focusing of ultrasound, curved crystals, lenses, and multiple beams have previously been utilized. In some of the experiments in this study, the cylinder-shaped plastic cup, which held the coupling medium and made contact with the brain surface, was changed to a cup of slight cone shape, the walls converging about 15 degrees. This further concentrated the beam through deflection of the sound from the walls toward the axis. With such a cup a certain degree of focusing effect was obtained, and the cone of concentrated damage then tended to penetrate deeper in the cerebrum and necrosis was produced after shorter exposure. For the purpose of studying the propagation of sound in brain tissue, excessively severe lesions were also made in some animals. It was remarkable that even a total necrosis which extended over more than half the cross section of a hemisphere spread mainly subcortically and tended to follow, but not to cross, the deeply curving line of demarcation between cortex and white matter (Fig. 1).

Comment.—Several factors could be given as contributing to the great variability of the brain lesions that developed after irradiation through the skull. The structure and thickness of the bone and the extent of the venous channels were inconstant, and the skin and the muscles varied in thickness from animal to animal and from one area of the same head to another. When the sound beam is directed through the skull at an angle with the perpendicular line, the refraction may be so great that part of the beam is totally reflected.

In previous reports the occurrence of brain necrosis in the form of a shallow cup had been explained in various ways. Lynn and associates [30] (1942) assumed that

it was due to the fact that their crystal had a spherical surface and that the sound beam was being focused thereby. Peters,[36] who obtained a similarly formed necrosis with a plane crystal, thought that the skull vault had a "focusing effect" and concentrated the beam toward the brain surface. However, in some of the experiments with nonfocused beams included here, neither the concavity of the crystal nor the cranium itself can be responsible, since a roughly cone-shaped area of necrosis could be produced despite the fact that the generator crystal was flat and the overlying skull bone had been removed. The cone-formed dispersement of sonic lesions within the brain itself may be due partly to the tendency of a stronger, central part of the ultrasonic beam to reduce in compass while it proceeds through homogeneous media.

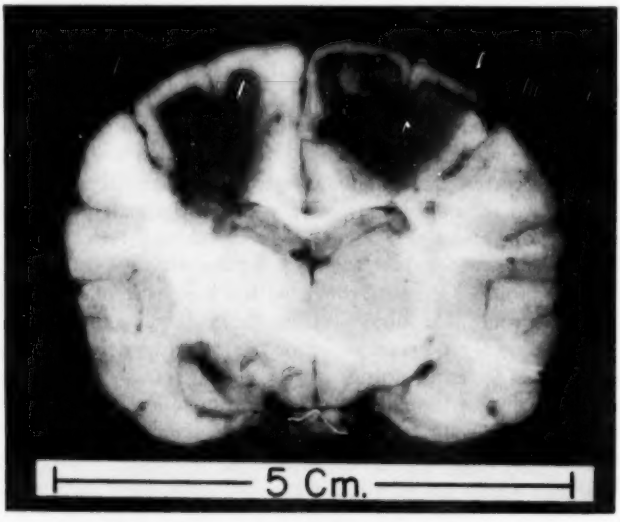

Fig. 1.—Excessive ultrasonic necroses which extended along the boundary between cortex and white matter in a dog brain. A nonfocused beam of 7 watts per square centimeter at 1,000 kc. per second was used. A dural flap was turned at the right side of the picture. On the opposite side the same irradiation was given through the intact dura.

Much of the superficial tissue destruction described in previous animal experiments in which the sound head rested directly on the tissue was probably caused by the moderate heat generated by the transducer at maximum output, rather than by the ultrasonic waves themselves. The thermal action of a warmed-up sound head, placed in contact with the skin or the brain, will, in turn, prevent an increase of exposure time and of sound energy necessary for the production of deep-seated lesions. It was only after the sound head was held in a cup filled with a transmitting fluid, such as saline, and when this solution was kept at room temperature by exchanging it at a rate of about 1,000 cc. every three to five minutes, and when the transducer was retracted at least 1 cm. from the brain, that cerebral lesions could be placed deep in the white matter, while the cortex and the meninges were preserved.

The effect of ultrasound tends to increase at the interface between media of different densities, and this is probably the main reason that, in transcranial irradi-

ation through an intact calvaria, the injury is concentrated at the meninges and the surface of the cortex. The accentuation of cell changes at the interface between cortex and white matter in direct irradiation may be explained in the same manner. It was a surprising observation that when the calvaria above had been trephined, necrosis was more readily developed in the white matter than in the cortex, although the latter was closer to the vibrating crystal (Fig. 1). Perhaps the richer blood supply of the cortex contributes to this increased resistance to direct sonic irradiation. The larger proportion of fat-rich myelin in the white matter might to some extent explain the heavier damage of the subcortex, since increased absorption of sound energy could be expected at the interface between myelin and tissue liquid.

The observations made in this study concerning the response of various cells and tissue elements probably apply to cerebral tissue in general. However, the degree and the spread of the damage were also influenced by the size and the shape of the brains and the architecture in their different parts. The sound did not proceed through the brains of rabbits and dogs in an entirely constant fashion. One could therefore expect that the path of the sound through the much larger human brain would differ somewhat from that in animals.

These experiments demonstrated that graded, controllable lesions, extending deep into the white matter, with comparatively little insult to the cortex of the exposed animal brain, could be produced by a single beam of ultrasound without noticeable ill-effects on the animals. The approach in the application of therapeutic tissue damage in humans was obviously to start with such small doses of radiation as, according to the animal studies, would cause only minute histological alterations; thereafter the dose could be increased as indicated. A total destruction extending over a large part of the cross section of the brain was to be avoided; on the other hand, a pinpoint necrosis placed somewhere in the prefrontal lobes would certainly not give a lobotomy effect. The question was whether a diffuse irradiation of ultrasound, graded to cause minimal histological changes and spread across part of the prefrontal areas, would affect the cerebral function of man and become clinically useful as a substitute for lobotomy. All indications were that the risk and complications from the application of ultrasonic energy, as used here, would be minor compared with those of operative lobotomies. The procedure was then carried out on human beings.

CLINICAL APPLICATION

On the basis of observations made in the animal experiments, it was decided to apply the sound in this clinical series through openings made in the calvaria.

With the patients in a half-sitting position, the superior part of the frontal bone was explored through a skin incision about 1 to 2 cm. anterior and parallel to the coronal suture or through parasagittal incisions. Bilateral trephine openings, 1¼ to 1½ in. (3.2 to 3.8 cm.), in diameter, were made over the frontal areas, reaching about 1 cm. anterior to the coronal suture and centered approximately in line with the pupils (Fig. 2). In the first nine cases small dural flaps were turned to expose the underlying cortex, but in all subsequent cases the dura was not opened. Prior to irradiation the patient was shifted to a sitting position so that the dorsal surface of the prefrontal lobes at the trephine level was slanting about 10 to 15 degrees forward. With the sound head fixed vertically the beam was aimed at the anterior tip of the lateral ventricle. Ringer's solution at room temperature, degassed by 20 minutes of boiling and continuously exchanged, acted as the coupling agent.

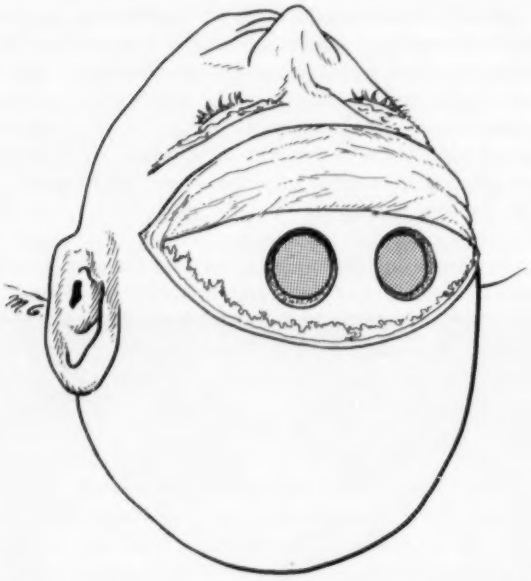

Fig. 2.—A bone button was removed over each prefrontal area through either one coronal or two parasagittal incisions. Transdural irradiation.

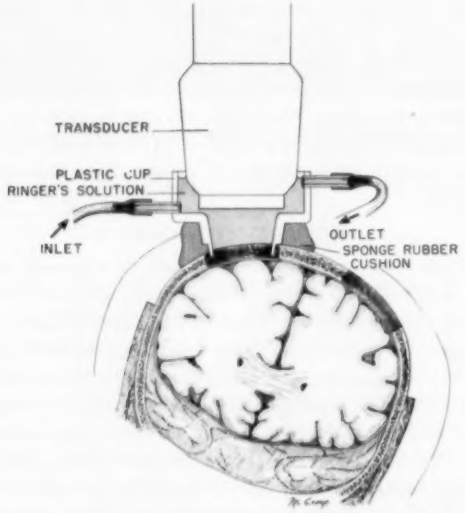

Fig. 3.—Diagram of the technical apparatus for transmission of ultrasound to the brain. In some patients the skull openings were made smaller.

In the first three cases the beam was directed via a light, cone-shaped plastic cup, with its smaller opening, 2 cm. in diameter, lightly placed against the brain surface to hold the transmitting liquid in place. In the next six cases a cup with a larger opening was held against the skull, while an attached sponge rubber ring gave a watertight connection; nothing but Ringer's solution was then in contact with the brain (Fig. 3). From then on no dural flaps were turned, nor was the dura incised or needled. In the earlier cases bleeders of the dura and cortical veins found attached to the dura were coagulated with the electrocautery. Later in the series such dural bleeding was controlled by gentle pressure or temporary application of absorbable sponges to avoid any possible cautery damage to the underlying brain surface.

A frequency of 1,000 kc. per second was used; the intensity averaged about 7 watts per square centimeter close to the crystal. The exposure time varied from 4 to 7 minutes over each lobe of the first nine patients; for the transdural irradiation this was extended to between 7 and 14 minutes, with some variations in intensity and concentration of the ultrasound. After adequate premedication the procedure was performed with use of local anesthesia in all 20 patients except 2, both of whom had thiopental (Pentothal) because of their discomfort in a sitting position.

CASE HISTORIES

In this first clinical series, of 20 patients,¶ selected for ultrasonic irradiation of the prefrontal region, 16 had intractable pain due to metastatic malignant tumors, often combined with anxiety, depression, and, in some instances, narcotic addiction. The 17th patient, with leukemia, had unbearable pain because of brachial plexus neuralgia and extensive x-ray reaction. The 18th patient, wasting from amyotrophic lateral sclerosis, had no pain but suffered from severe anxiety and, periodically, from profound depression. The 19th patient was a case of advanced Parkinsonism, with anxiety and heavy barbiturate addiction (1 to 1.5 gm. of secobarbital [Seconal] daily). The 20th patient, entirely unemployable owing to uncontrolled epilepsy of many years' duration, had become a serious behavior problem; he had spells of tantrums, and his frequent convulsions were often precipitated by emotional factors. All patients with malignant lesions had received maximum therapy in the form of surgery, x-ray irradiation, radioactive isotopes, cortisone, and other medication. Those with severe pain had been on large doses of opiates or other strong analgesics for long periods, with little relief. Before and after the ultrasonic irradiation the patients with malignant tumors were reviewed by the tumor board of the hospital. All but six were followed by a psychiatrist; five had psychological evaluation. Because of the poor general condition and the suffering of many of these patients, a number of desirable studies and tests could not be done. Electroencephalograms were taken on 15 patients after the ultrasonic treatment, and in 10 of these also before the treatment.

No postoperative complications occurred. All electroencephalograms were normal. There was no inertia, stupor, or incontinence, and no obvious personality changes, as a consequence of the ultrasonic irradiation. The patients retained their insight

¶ Five cases have been added and the follow-up periods extended as much as nine months since the original presentation of this paper in Helsinki, in 1953.

and judgment as far as could be estimated, and after their suffering was controlled or lessened, they took more interest in their surroundings and showed more initiative; several were able to go home.

Ten of the 17 patients suffering from excruciating pain had practically complete relief during periods of observation, which varied from 2 weeks to 11 months following the ultrasonic irradiation. Had they so desired, they could have continued their previous narcotic medication, but within one to three days after the irradiation either most of these patients did not ask for drugs or they themselves suggested that the narcotics be discontinued. All these patients appeared more relaxed, and some seemed slightly euphoric at times; most had better appetites. A few had return of pain, but it was then bearable, usually temporary, and often different in type and location. A differentiation between true organic pain and anxiety could not always be made, and in many instances there was a considerable overlap, with narcotic addiction also playing a part. It seemed that the relief was prompter and more striking when anxiety and emotional stress was a large component in the suffering. After the irradiation, small doses of barbiturates were often maintained, especially at night; additional narcotics were usually given at the terminal state.

Four other patients with intractable pain showed improvement in that the excruciating and persistent suffering they had experienced decreased after the prefrontal irradiation. They continued to be disturbed by intermittent moderate pain but were comfortable a good deal of the time, required less analgesic treatment, and appeared more relaxed. Of these 14 patients, 5 representative case histories are reported.

CASE 1.—Eleven months' observation after irradiation.

Clinical Data.—J. D.; age 32. Within four years after a myeloma had been diagnosed, the growth had metastasized to the ileum, ischium, ribs, both tibiae, and the skull. The patient had suffered from severe pain for the past 3 years and during the 12 months before admission had used 1.5 gm. of meperidine (Demerol) almost every 24 to 48 hours, administered by himself in the form of a hypodermic injection at 3- to 6-hour intervals. He worked fairly regularly up until September, 1952, when the pain became excruciating, especially in the pelvis, the right leg, and the head; a severe depression and insomnia developed, and he showed suicidal tendencies. By the time of his transfer to the neurosurgical service for the relief of intractable pain he was receiving ⅓ grain (20 mg.) of Pantopon every two to three hours, 1 grain (60 mg.) of codeine every three hours or ¼ grain (15 mg.) of morphine sulfate every two to three hours, and 4 fl. oz. (125 cc.) of wine every four hours, plus barbiturates. Even this medication gave him only partial and temporary relief.

Operation (May 18, 1953).—Prefrontal ultrasonic irradiation. Thiopental anesthesia was given because the patient could not sit still on account of his pain. Parasagittal trephine openings, 1½ in. in diameter, were made over the prefrontal regions; the margin of each trephine opening reached to within 1 cm. of the midline and 1 cm. anterior to the coronal suture. Small dural flaps were turned. The prefrontal lobes were irradiated with ultrasound of 7 watts per square centimeter at 1,000 kc. per second, aimed through the trephine openings in the direction of the anterior tip of the lateral ventricle on each side. The irradiation was thereafter widened in the coronal plane by aiming the beam about 30 degrees in the temporal direction for one minute on each hemisphere. The plastic cup holding the degassed Ringer's solution was slightly cone-shaped. The smaller opening of the cup was 2 cm. in diameter.

Postoperative Course.—When the patient had recovered from the anesthesia, he was alert and mentally clear. The pain had become much less intense. Within two days he was comparatively comfortable, and he himself suggested that the narcotics be discontinued. There was no loss of bladder control or other complication. On May 21 the chief of the medical service made the following note: "I have observed this patient frequently since his admission to the hospital. There has been a dramatic improvement since operation, on May 18. Patient is alert, cheerful,

entirely oriented, and almost free of pain." The consultant in neurosurgery made the following note on June 2: "This patient has been completely relieved of his pain since the ultrasonic lobotomy and has voluntarily stopped all his narcotics. His behavior in ordinary contacts on the ward seems entirely normal, and he shows no incontinence or lack of normal inhibitions and is cheerful and responsive with the nurses and attending physician. In general he seems to have exceptionally good results from his lobotomy." The patient started to gain weight. He was put in a plaster cast because of the destruction of the right acetabulum and was sent home on a 30-day furlough, still comfortable. On Sept. 31 he was discharged, but he returned to the hospital several times thereafter for reexamination. Psychological evaluation on Oct. 14 revealed "essentially good adjustments and normal reactions." An electroencephalogram on Oct. 9 was normal. Occasionally there was some pain of mild or moderate degree, but for about 11 months he was practically relieved of suffering. It was noteworthy that his headaches, even in mild form, never returned. In spite of good insight concerning his physical condition and prognosis and some very disturbing social problems that he had to cope with, this man retained the cheerful, cooperative attitude that followed the frontal lobe treatment. He took a greater interest in his surroundings, rearranged his insurance, and made plans for the future of his children, while before the irradiation he had been absorbed in his violent pains and his pitiful condition. Having remained rather comfortable and retained his weight gain for 11 months after the prefrontal treatment, he has begun to fail rapidly, owing to further spread of his tumor.

CASE 2.—Eleven weeks' postoperative observation.

Clinical Data.—L. S.; age 59. In May, 1953, a biopsy specimen from an inoperable abdominal tumor in the pancreas was diagnosed as scirrhous carcinoma. Because of intractable pain, gradually spreading over the whole abdomen and not controlled by opiates, and because of increasing mental depression, a prefrontal lobotomy was recommended by the Tumor Board of the hospital.

Operation (May 29, 1953).—Prefrontal ultrasonic irradiation with local anesthesia. Trephine openings, 1½ in. in diameter, were made over each prefrontal area as previously described and small dural flaps turned. Ultrasound of about 7 watts per square centimeter, slightly concentrated, was applied for five minutes on each side. The frequency was 1,000 kc. per second.

Postoperative Course.—Within a few hours following the ultrasonic irradiation there was a noticeable change in the patient's attitude. He became more relaxed and was resting fairly comfortably. Two days after this treatment all analgesics were discontinued because the patient had no further disturbing pains. An evaluation by the psychologist before the irradiation had demonstrated average intellectual capacity, with an I.Q. of 102. The psychological examination was repeated 12 days after the irradiation and the following conclusions reached: "The test results do not indicate any marked changes in intellectual functions, but there was a slight trend in the direction of improved function postoperatively. . . . He was alert and could concentrate adequately. . . . He remained rather comfortable and needed no further analgesics." In spite of his poor general condition both the patient and his relatives desired that he be cared for at home, since he had been relieved of his suffering, and on June 12 he was discharged from the hospital. The patient continued to be rather comfortable, did not need analgesics, and retained his mental capacities till shortly before death, Aug. 18, 1953.

Anatomical Findings.—Autopsy confirmed the diagnosis of cancer of the stomach and other abdominal organs. There was terminal bronchopneumonia. The brain showed no abnormalities except for some microscopic changes in the path of the sound beam in the prefrontal white matter (Fig. 4).

CASE 3.—Seven months' postoperative observation.

Clinical Data.—E. H.; age 64; diagnosis chronic lymphatic leukemia with extensive involvement of supraclavicular and axillary lymph nodes, leading to brachial plexus paralysis, which gradually made the whole left arm and hand paretic, numb, and aching. Painful roentgen-ray reaction of the neck and shoulder on the left side following radiation treatment in 1949. It was thought that his mental depression and his anorexia were to a considerable extent due to his shoulder and neck pain, which gradually had become nearly unbearable in spite of narcotics.

Operation (Aug. 4, 1953).—Prefrontal ultrasonic irradiation with use of local anesthesia. Trephine openings, 1½ in. in diameter, were made on each side. Small dural flaps were turned.

Five minutes' irradiation was given to each side, with sound intensity of about 7 watts per square centimeter at a frequency of 1,000 kc. per second. In addition, the irradiation was extended about 30 degrees in the temporal direction for two minutes on the right and for one minute on the left side.

Postoperative Course.—There were no postoperative complications. Bladder control and alertness were unimpaired. The psychologist reported that the patient was functioning at the lower limits of the average intellectual range but that there was no significant intellectual loss following the ultrasonic irradiation. The patient appeared relieved of his former suffering, although he sometimes was reluctant to admit that he was free of pain. His depression was definitely improved. Periodically he seemed irritable, particularly in conjunction with temporary flare-ups of pulmonary and urinary tract infections. From about November, 1953, he

Fig. 4 (Case 2).—Glial scar at the anterior tip of a lateral ventricle, with focal loss of ependymal lining. Magnification, × 120.

rarely complained of pains, and he retained a relaxed and cheerful attitude in spite of progressive loss of strength and weight. Electroencephalograms taken before and after operation were normal. In April, 1954, he showed great weakness, became apathetic, and gradually lost contact with his surroundings as his leukemia progressed. He died May 22, 1954.

Anatomical Findings.—The brain showed slight atherosclerosis of the basilar arteries, but otherwise no external abnormalities. (The brain is being prepared for serial sectioning.)

Case 4.—Nineteen days' observation after the irradiation.

Clinical Data.—J. A., age 60, was afflicted with cancer of the bladder with pelvic metastases, causing paraplegia and impaired bladder control; he suffered from intractable pain, localized mainly to the pelvis, and not controlled by heavy narcotic medication every three hours.

Operation (Oct. 19, 1953).—A prefrontal ultrasonic irradiation, using 7 watts per square centimeter at 1,000 kc. per second, was performed with local anesthesia. Trephine openings, 1½ in. in diameter, reaching 1 cm. anterior to the coronal suture, were made. The dura was

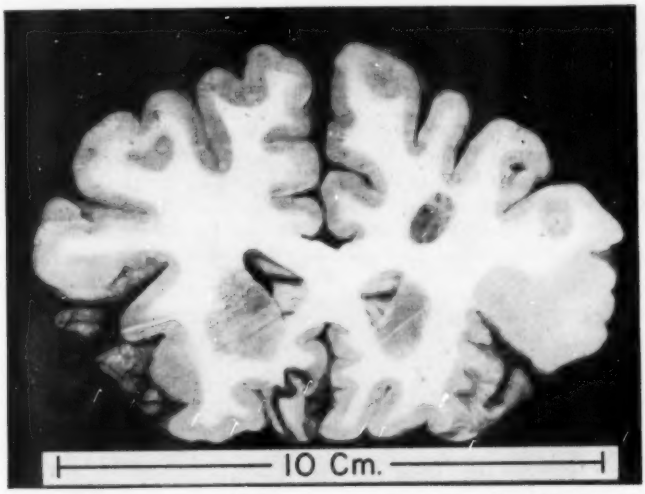

Fig. 5 (Case 4).—Ultrasonic necrosis in the centrum ovale on the right side of the picture. This section through the beam axis is directed about 15 degrees posteriorly. The center of the necrosis and the anterior tip of the ventricle are approximately in the same vertical plane. Autopsy 19 days after irradiation.

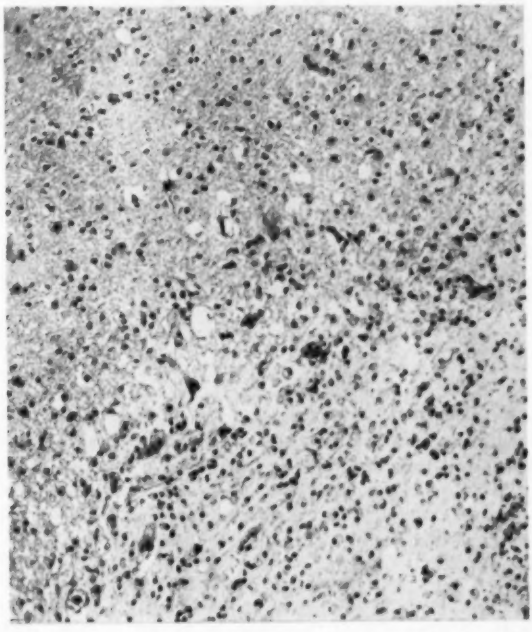

Fig. 6.—The margin of the necrosis shown in Fig. 4. Magnification, × 160.

not opened. Twelve minutes of ultrasonic irradiation was given on the right side in the direction of the anterior tip of the lateral ventricle. On the left side the radiation was given for eight minutes in the same direction; the left prefrontal lobe was, in addition, irradiated both in a more medial and in a temporal direction for two minutes, respectively, thereby widening the irradiated field in a coronal plane.

Postoperative Course.—There was no noticeable change in personality. The patient remained alert, with a clear sensorium. He behaved essentially as before and showed some concern about his downhill course but was more relaxed and did not suffer from his previous excruciating pains. Most of the narcotic medication could be discontinued. A dull ache of the abdomen and pelvic region disturbed him intermittently. He would ask for hypodermic injections at times, although less frequently than before. He insisted he felt "more at ease," and he certainly behaved

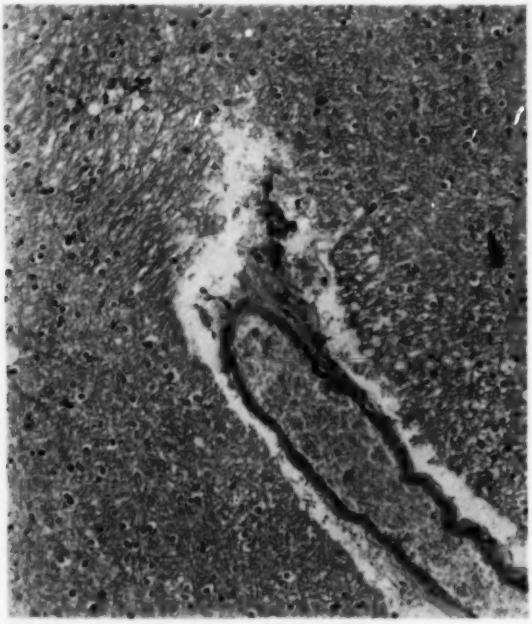

Fig. 7 (Case 5).—Perivascular ultrasonic necrosis with intracellular deposit of blood pigments. Magnification, × 160.

as though he did not suffer from much pain. Some days he took no narcotics at all; on other days, a grain (60 mg.) of codeine once or twice. Several times when he asked for "pain pills," he fell asleep within a few minutes before the medicine was given to him. In spite of long-standing sphincter disturbances combined with paraplegia, he was able, postoperatively, to control his urination until Nov. 4, when his general condition rapidly failed and a retention catheter was inserted; thereafter he showed signs of increasing pulmonary involvement. He died Nov. 7, 1953.

Anatomical Findings.—Extensive spread of the cancer in the pelvis and metastases to abdominal organs and lungs. A gross area of necrosis, 7 by 12 mm. in cross section, was found in the center of the white matter of the right prefrontal lobe at the level of the anterior tip of the ventricle. In the centrum ovale, on the left side only, some microscopic ultrasonic damage was seen (Figs. 5 and 6).

CASE 5.—Four weeks' observation after the irradiation.

Clinical Data.—J. S., age 63, had a carcinoma of the rectum with widespread metastases and was suffering from intractable pain, only partially relieved by large doses of narcotics. There was an obvious element of anxiety centering around the care of his colostomy and the appearance of a large, fungating inguinal metastasis.

Operation (June 20, 1953).—Prefrontal ultrasonic irradiation with local anesthesia. Three minutes of exposure was given on each side, with extension of the irradiation in the temporal direction for two minutes. A nonfocused beam of 7 watts per square centimeter at a frequency of 1,000 kc. per second was used, and dural flaps were turned.

Postoperative Course.—No complications occurred. The pain decreased promptly, and within a day the patient seemed relaxed and stated that his pain was gone. His preoperative urinary difficulties also improved noticeably. The patient did not ask for, nor did he require,

Fig. 8 (Case 5).—Slight gliosis at the level of the anterior tip of a lateral ventricle following ultrasonic irradiation. Magnification, × 120.

further analgesics. In mid-July he began a rapid downhill course, and seemingly without suffering, and died July 23, as a result of his extensive malignant disease (Figs. 7 and 8).

Anatomical Findings.—The clinical diagnosis was confirmed. The brain did not show any gross necrosis. Microscopically, there were scattered in the white matter some foci of necrosis in the vicinity of the beam axis. Blood pigments were also seen in a few places alongside vessels (Fig. 7). Microscopic alterations had also occurred at, and below the level of, the anterior tip of the ventricle (Fig. 8).

The remaining 3 of the 17 patients with intractable pain continued their complaints after the treatment. One of them was thought to be suffering considerably the first few weeks and received a second ultrasonic irradiation. It later became apparent that narcotic addiction was a large factor in his pain complaints; after a third irradiation he became fairly comfortable. The second patient had a short period of pain relief, but the ultrasonic treatment did not prevent a progression of

his depressed state after he saw his malignant disease spread rapidly. He died within four weeks. The third case was an obvious therapeutic failure. The case histories of these three patients follow.

CASE 6.—Eight months' observation after the irradiation.

Clinical Data.—V. F.; age 42. Laryngectomy was done in 1946 for carcinoma of the larynx; deep x-ray therapy followed. Early in 1953 a progressive weight loss and pain in the right side of the chest set in, and two tumor nodules were noted in the left lung field. The chest pains became severe and constant, and hypesthesia over the midportion of the right side of the chest developed. His general condition remained fair. Because of his intractable pains, only partially relieved by regular, large doses of narcotics, a lobotomy was recommended.

Operation (July 13, 1953).—Prefrontal ultrasonic irradiation. Trephine openings, 1½ in. in diameter, were made and small dural flaps turned. Four minutes of irradiation with an additional extension in the coronal plane for one minute, was given on each side, as previously described.

Postoperative Course.—The patient was alert, cooperative, and mentally clear; no personality changes were noted, and no incontinence or other complications occurred. An electroencephalogram taken one week after the operation was normal. The pain relief, which was not complete, lasted about two weeks. Thereafter he asked several times for meperidine, and gradually his requests for narcotics became more frequent. The irradiation was therefore repeated. An electroencephalogram taken July 22 was normal.

Second Operation (Aug. 22).—The same procedure was applied, using a wide, nonfocused beam through the previous trephine openings. The dura was not opened this time. Five minutes' irradiation was given bilaterally in the direction of the anterior tip of the ventricle, and 4 minutes' irradiation was directed more medially in the same coronal plane on each side.

Postoperative Course.—Again there were no definite personality changes, although the patient seemed more relaxed and jovial than before. No complications and no impairment of mental functions were noticed. He was up and about, enjoying recreation facilities, but periodically he complained of various pains in his chest, usually superficial; he stated repeatedly that the previous deep and excruciating pain was gone. He did not need the same amount of narcotics as before; local intercostal blocks with procaine relieved him of his temporary pains, and after a few such injections he said he did not need them. When he presented his complaints, he usually started with a smile and a joke. The general opinion of the several doctors who examined the patient was that he was rather comfortable, and that his complaints were in all likelihood based on narcotic addiction. Gradually the narcotic medication could be discontinued, and he was discharged Dec. 22. He gained weight, was able to do a little work around the house, and seemed to have no pain for about two more months. Thereafter he started to complain of vague pains, not the old severe ones but disturbing enough to require narcotics, and he was readmitted. An electroencephalogram taken Feb. 3, 1954, was normal. It was again the opinion of most observers that his complaints were based on craving for narcotics and difficulties in adjusting himself to a status of disability, and not so much on organic pains. It was, nevertheless, decided that the ultrasonic treatment be repeated.

Third Operation (March 5, 1954).—The ultrasonic irradiation was again repeated. A beam of 10 watts per square centimeter at 1,000 kc. per second slightly focused, was given in the direction of the anterior tip of the ventricle for two and one-half minutes on each side. The dural flaps were not opened.

Postoperative Course.—No inertia, incontinence, or other complications occurred. However, the trace of euphoria was more noticeable after this third treatment, though the patient retained a clear mind and good insight. He continued to complain periodically of pain but was up and about visiting frequently with patients on other wards; he could go weeks at a time without narcotics. He gained some weight, was sent home, and is now being cared for at home.

CASE 7.—One month's postoperative observation.

Clinical Data.—J. M., age 61. Cancer of the tongue was diagnosed by biopsy in October, 1952. In spite of maximum x-irradiation, the tumor spread so that it was found necessary to do

a bilateral radical neck dissection, with resection of the mandible and a large part of the tongue; a tracheotomy was also done. He suffered intractable pain in the neck and face in spite of large doses of narcotics.

Operation (June 24, 1953).—Prefrontal ultrasonic irradiation with local anesthesia. Trephine openings, 1½ in. in diameter, were made bilaterally, dural flaps were turned, and the brain was irradiated for five minutes on each side with an intensity of about 7 watts per square centimeter, the beam being slightly focused and the treatment extended in the temporal direction for about one minute.

Postoperative Course.—The patient retained his mental functions, his alertness, and his previous behavior. There were no convulsions, incontinence, or other complications. For the first postoperative days he had little or no pain. The following 10 days he got along well on small doses of barbiturates every 12 hours. He was even given some occupational therapy, for which he had shown no cooperation previously. Thereafter, there was a gradual return of moderate pains in the face and neck. About July 6 the pain became severer, and progressive

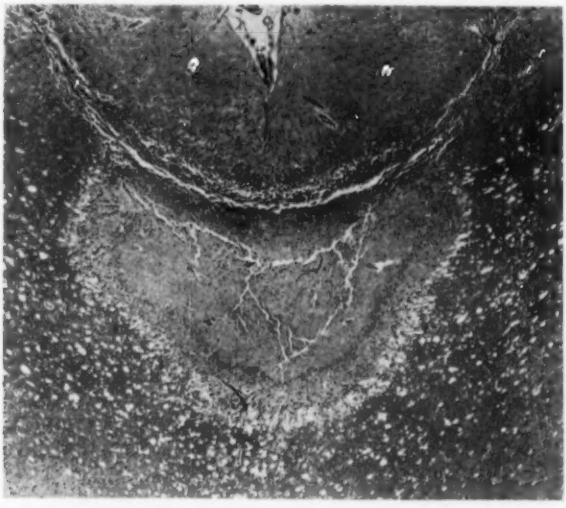

Fig. 9 (Case 7).—Single area of gross subcortical necrosis, below a sulcus, 2 cm. deep, which descends from the superior surface of the prefrontal lobe. The neighboring gyri, closer to the vibrating crystal, did not show any necrosis. Magnification, × 32.

ulcerations inside the mouth started to bleed, which upset the patient a great deal. From then on the tumor spread rapidly. It became almost impossible for the patient to swallow or talk. A gastrostomy had to be performed on July 17, 1953; the patient went into a severe depression, and from then on it was hard to say whether he suffered more from his pains or from his depression. He was again given rather large doses of narcotics more or less regularly, and after a rapid turn for the worse he died, July 26, 1953.

Anatomical Findings.—Extensive spread of the cancer regionally, and also to the kidneys. A terminal bronchopneumonia had occurred. The brain showed a subcortical gross area of necrosis, 2 by 3 mm., in a coronal section through the beam axis (Fig. 9). Other abnormalities were only microscopic ones in the white matter where the sound had passed through. For example, a cellular reaction in scattered areas was seen, more so along capillaries and sometimes only on one side of a vessel (Fig. 10).

CASE 8.—Five months' observation after irradiation.

Clinical Data.—J. McK., 58 years old, had a six-month history of an epidermoid carcinoma in the right supraclavicular fossa and severe pain in the right arm. In spite of maximum therapy

with roentgen rays, the tumor increased locally, producing a brachial plexus paralysis, with excruciating, constant pain, uncontrolled by heavy doses of narcotics. The Tumor Board advised lobotomy.

Operation (July 1, 1953).—Prefrontal ultrasonic irradiation with local anesthesia. Parasagittal trephine openings, 1½ in. in diameter, were made and small dural flaps turned. An average intensity of 7 watts per square centimeter was applied for four minutes to each prefrontal lobe. During an additional one-minute treatment, the irradiation was extended in the temporal direction on each side.

Postoperative Course.—The patient retained memory, alertness, and mental functions. No personality changes were noted. There was evidently some relief of pain the first 10 days, but soon thereafter the pain returned to almost its preoperative intensity.

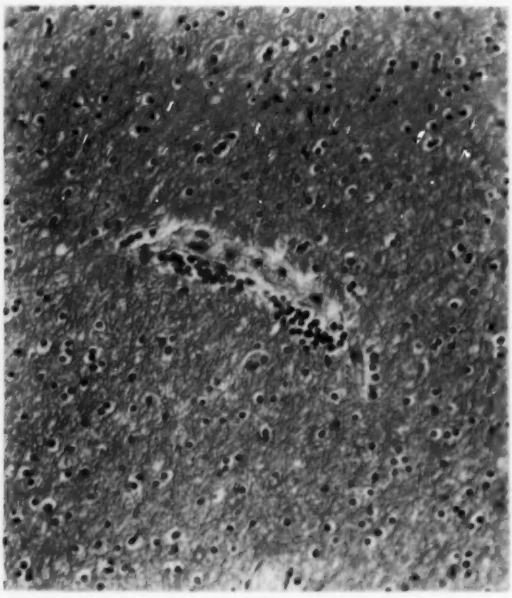

Fig. 10 (Case 7).—Accumulation of glial cells along one side of a vessel in the path of an ultrasonic beam. Magnification, × 220.

Second Operation (July 17, 1953).—Prefrontal ultrasonic irradiation with local anesthesia. Five minutes' irradiation was given on each side in the direction of the anterior tip of the ventricles.

Postoperative Course.—Again a minor improvement occurred for some days, but within a couple of weeks the pain had become almost as severe as before the first treatment and periodically it seemed just as bad. The patient was cooperative, retained good insight, and appeared sensible and objective in his judgment. His behavior seemed normal, but there was no euphoria. Narcotic addiction did not seem to be a factor in this case; the treatment simply did not give this patient the expected relief and he continued to suffer severely, as the narcotics could help him only partially. After the patient had lost much weight and strength, the ulcerating tumor suddenly caused a rupture of the right subclavian artery and a fatal hemorrhage on November 28.

Anatomical Findings.—Extensive destruction and necrosis from the epithelial cancer, which apparently was primary in the right supraclavicular fossa. The brain showed slight hemorrhagic

discoloration where the dural flaps had been turned and minor excoriation of the underlying cortex, probably from cauterization of cortical and dural bleeders. In the central ovale there were also areas of minimal histological changes in the path of the sound beam.

AUTOPSY STUDIES

Fifteen patients died within 19 days to 7 months following the irradiation, owing to spread of their malignant growths. Autopsies were performed on all of them, but in one the brain was not obtained. The clinical diagnosis of a malignant neoplasm was confirmed in each of these cases. No cerebral metastases were found, and none of the sonic brain lesions encountered was of such a degree or so located as to be suspected of having contributed to death. Representative sections from irradiated areas and, for control purposes, from other parts of the formalin-hardened cerebral hemispheres were examined microscopically. A more complete report of the pathology of ultrasonic brain lesions in humans is to be published.

Gross Anatomy of the Brains.—Externally, most brains showed no abnormalities. The basilar arteries had undergone moderate atherosclerosis in two specimens. A superficial hemorrhagic discoloration and small spots of necrosis with barely visible loss of substance to a depth of about 1 mm. of the cortex were noted in five cases just where the dural flaps had been turned. Such surface defects were probably due to electrocoagulation of cortical vessels which had been bleeding or had been attached to the dura.

The most striking findings in these 14 brains were the minimal structural alterations that had taken place in the path of the sound beam and the greater sensitivity of the subcortex. If one disregards the surface changes under some of the dural flaps, which in all likelihood were not caused by the sound itself, most of the hemispheres treated appeared normal. Several brains of patients who had responded very well to the treatment showed no visible damage to either frontal lobe. Even the patient who had been irradiated twice and come to autopsy (Case 8) had a grossly normal brain. In other specimens, the narrow band of yellow-brownish discoloration following the boundary between cortex and white matter, and described in the report on animal studies, was found. Such subcortical color bands, duplicating the silhouette of the gyri and sulci, could not have been caused by heat from the sound head, because they sometimes faded toward the top of the gyri.

Two hemispheres showed a demarcated, gross area of necrosis, in both cases localized to the white matter. The largest one, lying in the middle of the centrum ovale, measured 7 by 14 mm. (Fig. 5). A similar, but smaller, destruction, 2 by 3 mm., was seen below a deep sulcus in one case (Fig. 9). A cleft-like space, only 1 by 2 mm. in cross section, was found in a third centrum ovale and probably represented an ultrasonic lesion. The irradiation of the human brains had not been so intensified as to cause the extensive destruction produced in some of the animals. No cerebral hemorrhages or cysts were found. No mutilation of the prefrontal lobes occurred.

Microscopic Examination of the Brains.—A more complete discussion of the histopathology is being postponed until a larger number of transdurally irradiated brains have been studied in which the dura was neither opened nor cauterized. In

The histological material has been prepared by the Department of Pathology, Veterans Administration Hospital, Pittsburgh.

such specimens any meningeal or cortical alterations caused by ultrasound will not be confused with the damage that may follow thermocoagulation of bleeders in or under the dura. Some general observations of the histopathology will, however, be reported here.

A few prefrontal lobes seemed undamaged or showed such minimal histological alterations that one probably would have considered the sections normal if they had not been compared with areas outside the irradiated zone. The first tissue elements that reacted anatomically to increasing sound levels were the fiber tracts and the ganglion cells. The most frequent changes were seen scattered in the white matter through which the sound beam had passed; these were in the form of a

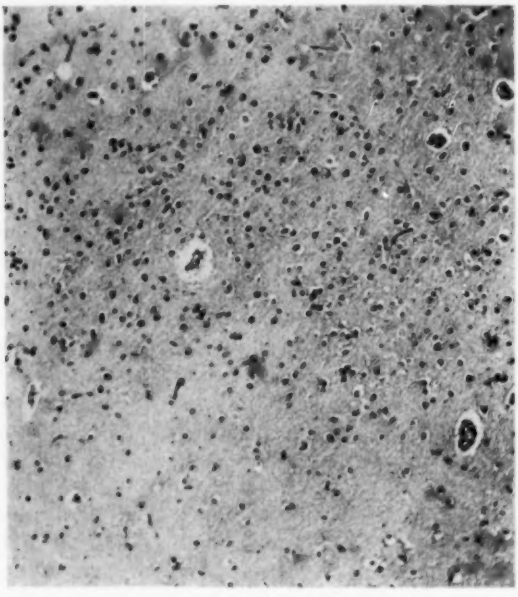

Fig. 11.—Human prefrontal cortex. An ultrasonic beam of 7 watts per square centimeter at 1,000 kc. per second, directed from above, had passed through this section taken from the bottom of a parasagittal sulcus. The ganglion cells have disappeared. No gross necrosis seen in this brain. Autopsy two months after irradiation. Magnification, × 160.

slight increase of glial cells, microscopic glial scars, disfigurement and disruption of myelin sheaths, and minute cleft-like spaces. In many instances, the cortex was normal; in others, ganglion cells were lost in the path of the beam or were in various stages of degeneration, while the cortex still retained its general architecture (Fig. 11). Here and there in the subcortex one saw an increase of glial cells along a vessel. Such cell accumulation was sometimes confined to one side of a vessel (Fig. 10), and not in the form of a cuffing, as is commonly the case in inflammations. With increasing sound energy, occasional groups of red blood cells found their way through the vessels. This had apparently taken place after comparatively minor damage to vessel walls, because most vessels retained their symmetry and normal lamination at this stage. Residuals of that process were manifested after

longer postirradiation survival by a few minute deposits of blood pigments, spread along seemingly intact vessels. At even higher sound levels areas of necrosis developed, involving all tissue elements.

Where the beam had passed through the white matter, one could at times see progressive repair in the form of capillary proliferation, small deposits of hyalinized astrocytes, compound granular corpuscles, and minor glial scars imbedded in otherwise normal-appearing brain tissue. Inflammatory reactions, even around patches of necrosis, were conspicuously minimal. Where the insult reached the stage of destruction, it had the characteristics of colliquation rather than a coagulation necrosis. As a whole, the microscopic picture resembled the late manifestations of a mechanical trauma more than any other form of brain injury. No anatomical damage was found in the human brains outside the path of the beam. (Late retrograde degeneration of fiber tracts and secondary changes in distant nuclei were not investigated at this time but can be expected to occur in specimens with a gross necrosis.)

COMMENT

Morphological Aspects.—The mechanism of the biological action of ultrasound is poorly understood, just as our knowledge of how x-rays and radium destroy living tissues is quite incomplete. An interesting selective effect of ultrasound on some tissue elements and certain strata of the brain was described and discussed in the foregoing report.

It was observed, both in the animal and in the human specimens, that sonic damage may be microscopically found scattered in structurally normal white matter within the range of the ultrasonic beam. This phenomenon could hardly be explained on the basis of increased absorption of sound energy at interfaces, since the white matter is architecturally rather uniform. A variation in "micromassage" at nodes and antinodes of these longitudinal, high frequency mechanical waves, about 1.5 mm. long, might contribute to this peculiar pattern. The greater "sensitivity" of the ganglion cells in comparison with glial elements may be due partly to the larger size of the neurons.

In view of the great number of lobotomies reported, perhaps 25,000 in the United States and perhaps the same number in Europe, the published autopsy material is surprisingly small, especially considering the widespread use of this procedure for relief of pain due to malignant neoplasms. The few neuroanatomical studies of lobotomies available consistently demonstrate great variability and often excessive degrees of destruction in the frontal lobes. Judging from those reports, covering only a small fraction of all lobotomized patients, one can say that the cerebral damage in the 14 necropsies included in this study is less variable and much less severe than in lobotomies.

It is reasonable to ask how the symptomatic improvement obtained here could have been produced by ultrasonic irradiation when the tissue alterations generally were comparatively mild. One explanation is that the microscope often gives a poor picture of the pathophysiological activities of tissues. There may be considerable functional abnormalities in the living cells which are not manifest in the formalin-fixed and stained specimens. Where the ultrasound has passed, fiber tracts and brain cells may have been more altered than is evident in the microscope. There may be, for example, cellular changes in the brains of imbeciles and persons with

severe psychoses, although histologically their central nervous systems often appear normal. Even when a postconcussion syndrome has been severe, including electroencephalographic dysrhythmia and epilepsy, the brain sections may show no abnormalities. Iobst and Forster [69] emphasized that the absence of an anatomic disorder does not militate against an electroencephalographic focus, and they pointed out that the nature of an epileptogenic lesion "is beyond the present boundaries of histopathologic technique."

Obviously, there is a factor of unintentional variability in the aiming of the sound with this technique. It would seem, however, that the sound beam can be directed through the brain with less uncertainty than can the leucotome or the suction tip. The location and shape of the gross necrosis, which was visible in two of the autopsy specimens, proved that the maximum damage had developed in the direction of the anterior tip of the ventricle; the spread of the microscopic lesions in other cases gave the impression that the beam had passed approximately in the same direction. A more exact placement of the sound beam may, of course, be accomplished with a stereotactic instrument, but then the simplicity of this procedure would be lost.

More important than the comparative accuracy of the direction of the beam was the fact that the autopsies showed tissue changes only inside the path of the beam and none of the parasurgical destruction which may occur in lobotomies. Directing the sound into the ventricles does not in itself carry the same risks as an actual cut through them. There is no evidence that the extension of a moderately intense irradiation to a part of the ventricular wall causes any complications; in the cases in which a histological damage had reached the anterior tip of a ventricle, no untoward symptoms were noticed.

Clinical Results and Their Evaluation.—The various lobotomy operations are the same in principle and are performed in the same manner, whether they are intended for the relief of mental symptoms or for control of pain. Experience has shown that if a certain form of lobotomy is of value in intractable pain and anxiety, then it is also of value in the types of psychoses that usually respond to psychosurgery. In this investigation, the clinical material has purposely been limited, with few exceptions, to patients with inoperable malignant growths. A high percentage of autopsy specimens has become available and thus has assured an objective control of the amount of damage administered. The method is now being further standardized so that a certain histological alteration in the centrum ovale can be predicted and graded on the basis of sound intensity and exposure time. The indications for prefrontal ultrasonic irradiation may then be extended to patients with certain mental disorders who are not suffering, in addition, from malignant disease.

Some authors describe a more or less complete relief of pain in 80 to 100% of cases following lobotomies. A report by Howarth and Gardner,[70] in 1952, probably better reflects the actual results than other, more optimistic claims. These authors list their 25 cases thus: Results—good 11, fair, 5, poor 7, fatal 2." The part that the lobotomy plays as a contributing factor in the death of patients with malignant neoplasms must necessarily increase when those in poor condition are included, when a general anesthesia is given, and when more extensive cuts are made.

One should not expect too much in the way of relief of suffering among cancer patients from therapeutic damage of prefrontal tissue. Practically no patient who

remains rational, while failing because of a spreading malignant neoplasm, will be comfortable until his death, no matter how "successful" the treatment of pain has been. Malaise, nausea, vomiting, incontinence, abdominal distention, dyspnea, severe weakness, a cachectic appearance, and all the things that remind the patient of the steady progression of his illness will continue to disturb him to some degree after any form of lobotomy if he retains good insight and judgment. By "improvement" in these patients with metastases is meant the relief of severe, constant pain; the lessening of emotional tension, fears and worries, and marked reduction or elimination of need for narcotics. The impression of the several observers who have followed the patients is that the results in this series compare favorably with those obtained with surgical lobotomies in similar cases; all observers have noted the lack of side-effects.

The fact that none of these patients has had any convulsions, that cortico-meningeal scars have not occurred, that the dura need not be opened, and that the cortex can be spared and the main damage placed in the white matter would indicate that convulsions should be rare. It is significant that the electroencephalograms, taken postoperatively in 15 patients, all showed normal tracings, while this test is almost always abnormal following lobotomies.

Reversible Effect; Further Development.—Wood and Loomis [20] (1927) found that mice which could not move immediately after supersonic irradiation, later became active again. Functional recovery of the animal spinal cord, following its irradiation, has been related by a few authors.* Heyck and Höpker [35] found that cells of the rat brain could recover from certain microscopic damage by sound. In the present study, observations on animals which survived 1 to 28 days after irradiation indicated that minor histological reactions of the brain to ultrasound are reversible. There is ample evidence from clinical neurosurgery that the brain at times will recover from even serious mechanical trauma, and the histological picture of ultrasonic brain lesions resembles that of trauma, more than that of any other form of insult. In fact, one can in some respects compare this ultrasonic treatment with a cerebral concussion limited to part of the prefrontal lobes. On the basis of further clinical and pathological data, it should be possible to predict with some degree of accuracy whether the effect of a certain ultrasonic irradiation will last only for days, or will persist for many months, or will become permanent. It would then be possible to use the treatment in a preliminary test, to repeat the procedure with increased sound energy, if so indicated, and to cause more lasting results when desired.

The method applied in this investigation obviously needs further improvement. The skin incision does not bother the patients; the irradiation itself is painless, except that a few patients have had some local meningeal pain at the beginning of the exposure. Trephining the skull, on the other hand, now takes up a good deal of the time needed for the application of ultrasound, and the patients sometimes complain of the noise and the shaking. With higher sound levels the exposure time could be shortened and the trephine openings be made smaller.† A burr hole

* References 31, 52, and 63.

† In further studies on animals and human beings, not included in this report, the irradiation time has been shortened considerably by using a beam of higher intensity, 12 watts per square centimeter, more or less focused.

can be done so much easier and faster than a 1 to 1½ in. bone button that such a change alone would simplify the procedure. Sufficient effect should then be obtained in 30 to 60 seconds from a single crystal and a concentrated, narrow beam. It is still questionable, however, whether such an intense application is preferable to a weaker and less focused beam, requiring longer exposure.

Multiple ultrasonic beams focused on the prefrontal lobes through the intact skull might possibly give enough damage of the brain for a lobotomy effect without causing necrosis to the skin; it seems doubtful whether such a transcranial irradiation can be standardized so that the amount of damage could be predicted with desirable accuracy. A multiple beam outfit, as suggested by Dussik,[44] for production of a focal necrosis would have restricted use in clinical neurosurgery, since it would require several trephines or a large bone flap to avoid the scattering of the sound by the skull.

A number of patients, even among carefully selected groups, will not show any improvement in mental symptoms or any relief in pain from a lobotomy, regardless of the extent of coagulation or cutting. The accumulated evidence from many hundreds of reports has given us an idea of what can be accomplished by lobotomies in a large series. There is at this time no means of predicting the symptomatic improvement after lobotomy or a prefrontal ultrasonic irradiation in the individual case. One can, however, assure the patient and his relatives that the chances of complications or of accentuation of symptoms are minimal with this ultrasonic treatment, since the therapeutic damage is controlled and unintentional mutilation can be avoided.

SUMMARY

Transcranial and direct irradiation of the animal brain with high frequency sound was studied. A technique was developed for the production of graded subcortical lesions.

Therapeutic ultrasonic damage to the prefrontal lobes was applied to human beings as a substitute for lobotomy. Eight case histories representative of a series of 20 patients are reported. The procedure is comparatively simple, carries a minimal risk, and has, among this limited number of patients, given clinical results that compare favorably with those of surgical lobotomies in similar cases.

Fifteen of the patients treated for intractable pain due to malignant tumors later succumbed to their diseases, and 14 complete necropsies were performed. The histological damage in the path of the sound beam was localized mainly to the white matter. A satisfactory lobotomy effect was obtained in most cases in spite of the fact that the tissue alterations were minimal. The ultrasonic damage can be controlled and graded, from a reversible or minimal effect to a gross necrosis in the subcortex, without opening the dura. Unintentional mutilation can be avoided.

REFERENCES

1. Beck, E.; McLardy, T., and Meyer, A.: Anatomical Comments on Psychosurgical Procedures, J. Ment. Sc. **96**:157-167, 1950.

2. Grünthal, E.: Über die anatomischen, physiologischen und pathologischen Grundlagen der frontalen Leukotomie, Monatsschr. Psychiat. u. Neurol. **119**:361-377, 1950.

3. McLardy, T.: Uraemic and Trophic Deaths Following Leucotomy: Neuro-Anatomical Findings, J. Neurol., Neurosurg. & Psychiat. **13**:106-114, 1950.

4. Meyer, A., and McLardy, T.: Posterior Cuts in Prefrontal Leucotomy: Clinicopathological Study, J. Ment. Sc. **94**:555-564, 1948.

5. Stjernberg, F.: Pneumoencephalographic Findings in Some Cases of Leucotomy, Acta psychiat. et neurol. scandinav. (Supp.) **47**:400-415, 1947.

6. Glees, P.; Cole, J.; Whitty, C. W. M., and Cairns, H.: Effects of Lesions in the Cingular Gyrus and Adjacent Areas in Monkeys, J. Neurol., Neurosurg. & Psychiat. **13**:178-190, 1950.

7. Raskin, N.; Strassman, G., and Van Winkle, C. C.: Neuropathologic Lesions Following Lobotomy: Study of 15 Cases of Bilateral Prefrontal Lobotomy, Am. J. Psychiat. **109**:808-816, 1953.

8. Wohlfahrt, S.: Psychiatric Views on Problem of Leucotomy, Acta psychiat. et neurol. scandinav. (Supp.) **47**:348-360, 1947.

9. Yakovlev, P. I.; Hamlin, H., and Sweet, W. H.: Frontal Lobotomy: Neuroanatomical Observations, J. Neuropath. & Exper. Neurol. **9**:250-285, 1950.

10. Dax, E. C.; Reitman, F., and Radley-Smith, E. J.: Prefrontal Leucotomy, Digest Neurol. & Psychiat., Inst. of Living, **16**:533, 1948.

11. Fulton, J. F.: Frontal Lobotomy and Affective Behavior, New York, W. W. Norton & Company, Inc., 1951.

12. Grantham, E. G., and Spurling, R. G.: Selective Lobotomy in the Treatment of Intractable Pain, Ann. Surg. **137**:602-608, 1953.

13. Greenblatt, M.; Arnot, R., and Solomon, H. C., Editors: Studies in Lobotomy, New York, Grune & Stratton, Inc., 1950.

14. Hofstatter, L.; Smolik, E. A., and Busch, A. K.: Prefrontal Lobotomy in Treatment of Chronic Psychoses, with Special Reference to Section of the Orbital Areas Only, Arch. Neurol. & Psychiat. **53**:125-130, 1945.

15. Pool, J. L.; Heath, R. G., and Weber, J. J.: Topectomy: Surgical Indications and Results, Bull. New York Acad. Med. **25**:335-344, 1949.

16. Rylander, G.: Therapeutic Results of Different Types of Frontal Lobe Operation, Acta psychiat. et neurol. scandinav. (Supp.) **80**:122-128, 1952.

17. Sargent, W.: Ten Years' Clinical Experience of Modified Leucotomy Operations, Brit. M. J. **2**:800-803, 1953.

18. Scoville, W. B., and others: Observations on Medial Temporal Lobotomy and Uncotomy in the Treatment of Psychotic States, A. Res. Nerv. & Ment. Dis., Proc. (1951) **31**:347-369, 1953.

19. Thorpe, F. T., and Hardman, J.: Lower Quadrant Leucotomy, J. Ment. Sc. **98**:389-400, 1952.

20. Tow, P. M., and Whitty, C. W. M.: Personality Changes After Operations on the Cingulate Gyrus in Man, J. Neurol., Neurosurg. & Psychiat. **16**:186-193, 1953.

21. Whitty, C. W. M.; Duffield, J. E.; Tow, P. M., and Cairns, H.: Anterior Cingulectomy in the Treatment of Mental Disease, Lancet. **1**:475-481, 1952.

22. Burckhardt, G.: Über Rindenexcisionen, als Beitrag zur operativen Therapie der Psychosen, Allg. Ztschr. Psychiat. **47**:463-548, 1890-1891.

23. Egas Moniz: Tentatives opératoires dans le traitement de certaines psychoses, Paris, Masson & Cie, 1936.

24. Fisher, R. G.: Psychosurgery, in Walker, A. E., Editor: A History of Neurological Surgery, Baltimore, Williams & Wilkins Company, 1951, Chap. 11.

25. Freeman, W., and Watts, J. W.: Psychosurgery in the Treatment of Mental Disorders and Intractable Pain, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1950.

26. Wood, R. W., and Loomis, A. L.: Physical and Biological Effects of High Frequency Sound Waves of Great Intensity, Philos. Mag. **4**:417-436, 1927.

27. Harvey, E. N., and Loomis, A. L.: High Frequency Sound Waves of Small Intensity and Their Biological Effects, Nature, London **121**:622-624, 1928.

28. Schmitt, F. O.; Olson, A. R., and Johnson, C. H.: Effects of High Frequency Sound Waves on Protoplasm, Proc. Soc. Exper. Biol. & Med. **25**:718-720, 1928.

29. Lynn, J. G.; Zwemer, R. L., Chick, A. J.: Biological Application of Focused Ultrasonic Waves, Science **96**:119-120, 1942.

30. Lynn, J. G.; Zwemer, R. L.; Chick, A. J., and Miller, A. E.: New Method for the Generation and Use of Focused Ultrasound in Experimental Biology, J. Gen. Physiol. **26**:179-193, 1942.

31. Lynn, J. G., and Putnam, T. J.: Histology of Cerebral Lesions Produced by Focused Ultrasound, Am. J. Path. **20**:637-649, 1944.

32. Allegranza, A.: Effetti distruttivi degli ultrasuoni sul sistema nervoso centrale, Biol. latina **3**:454-468, 1950.

33. Gregg, E. C., Jr.: Ultrasonics: Biologic Effects, in Glasser, Otto, Editor, Medical Physics, Chicago, The Year Book Publishers, Inc., 1944, Vol. I, pp. 1591-1596.

34. Leonhardt, H.: Untersuchungen über die Einwirkung von Ultraschall auf das Gehirn, Med. Klin. **44**:1162-1163, 1949.

35. Heyck, H., and Höpker, W.: Hirnveränderungen bei der Ratte durch Ultraschall, Monatsschr. Psychiat. u. Neurol. **123**:42-64, 1952.

36. Peters, G.: Experimentelle Ultraschallschäden am Gehirn, Ultraschall in Med. **4**:60-62, 1952.

37. Wall, P. D.; Tucker, D.; Fry, F. J., and Mosberg, W. H., Jr.: Use of High Intensity Ultrasound in Experimental Neurology, J. Acoust. Soc. Am. **25**:281-285, 1953.

38. Zubiani, A.: Sull'applicazione della energia ultrasonora al sistema nervoso centrale, Minerva med. **1**:421-436, 1951.

39. Denier, A.: Ultra-sons et diencéphale, J. radiol. et électrol, **29**:278-279, 1948.

40. Heyck, H.: Ultraschall und Zentralnervensystem, Schweiz. med. Wchnschr. **82**:97-99, 1952.

41. Ballantine, H. T., Jr.; Ludwig, G. D.; Bolt, R. H., and Hueter, T. F.: Ultrasonic Localization of the Cerebral Ventricles, Tr. Am. Neurol. A. **75**:38-41, 1950.

42. Langevin, M. P.; Chilowsky, N. C., and Tournier, M.: Emission d'un faisceau d'ondes ultra sonores par excitations piezoelectriques d'une lame de quartz en resonance, J. physiol. **4**:537-539, 1923.

43. Ballantine, H. T., Jr.; Bolt, R. H.; Hueter, T. F., and Ludwig, G. D.: On the Detection of Intracranial Pathology by Ultrasound, Science **112**:525-528, 1950.

44. Dussik, K. T.; Dussik, F., and Wyt, L.: Auf dem Wege zur Hyperphonographie des Gehirnes, Wien. med. Wchnschr. **97**:425-429, 1947.

45. Dussik, K. T.: Weitere Ergebnisse der Ultraschalluntersuchung bei Gehirnerkrankungen, Acta. neurochir. **2**:379-396, 1952.

46. French, L. A.; Wild, J. J., and Neal, D.: Detection of Cerebral Tumors by Ultrasonic Pulses, Cancer **3**:705-708, 1950.

47. Hueter, T. F., and Bolt, R. H.: Ultrasonic Method for Outlining the Cerebral Ventricles, J. Acoust. Soc. Am. **23**:160-167, 1951.

48. Harvey, E. N.; Harvey, E. B., and Loomis, A. L.: Further Observations on the Effect of High Frequency Sound Waves on Living Matter, Biol. Bull. **55**:459-469, 1928.

49. Pätzold, J., and Born, H.: Behandlung biologischer Gewebe mit gebundeltem Ultraschall, Strahlentherapie **76**:486-492, 1947.

50. Lepeschkin, W. W., and Goldman, D. E.: Effects of Ultrasound on Cell Structure, J. Cell. & Comp. Physiol. **40**:383-397, 1952.

51. Goldman, D. E., and Lepeschkin, W. W.: Injury to Living Cells in Standing Sound Waves, J. Cell. & Comp. Physiol. **40**:255-268, 1952.

52. Fry, W. J.; Wulff, V. J.; Tucker, D., and Fry, F. J.: Physical Factors Involved in Ultrasonically Induced Changes in Living Systems: I. Identification of Non-Temperature Effects, J. Acoust. Soc. Am. **22**:867-876, 1950.

53. Fry, W. J.: Action of Ultrasound on Nerve Tissue: A Review, J. Acoust. Soc. Am. **25**:1-5, 1953.

54. Bender, L. F.; Herrick, J. F., and Krusen, F. H.: Temperatures Produced in Bone by Various Methods Used in Ultrasonic Therapy, Arch. Phys. Med. **34**:424-433, 1953.

55. Herrick, J. F.: Temperatures Produced in Tissues by Ultrasound: Experimental Study Using Various Technics, J. Acoust. Soc. Am. **25**:12-16, 1953.

56. Lehmann, J. F.: Biophysical Mode of Action of Biologic and Therapeutic Ultrasonic Reactions, J. Acoust. Soc. Am. **25**:17-25, 1953.

57. Harvey, E. N.: Biological Aspects of Ultrasonic Waves, Biol. Bull. **59**:306-325, 1930.

58. Veltman, G.: Bakterizide und immunbiologische Wirkungen des Ultraschalls, Ultraschall in Med. **2**:22-28, 1950.

59. Grabar, P.: Biological Action of Ultrasonic Waves, in Lawrence, J. H., and Tobias, C. A., Editors: Advances in Biological and Medical Physics, New York, Academic Press, Inc., 1953, Vol. 3, pp. 191-246.

60. Hesselberg, I.: Investigations on the Effect of Ultrasonics on Bacteria, Acta path. et microbiol. scandinav. (Supp.) **93**:389-399, 1952.

61. Rekaa, A.: Ultrasonics Applied to Biological Research: Experimental Technique and Measurement of the Intensity of Ultrasonic Waves, Acta path. et microbiol. scandinav. (Supp.) **93**:384-388, 1952.

62. Schikorski, K.: Der neurale Wirkungsmechanismus des Ultraschalls im Lichte einer tragfähigen Nervenfunktionstheorie, Strahlentherapie **87**:556-566, 1952.

63. Anderson, T. P., and others: Experimental Study of the Effects of Ultrasonic Energy on the Lower Part of the Spinal Cord and Peripheral Nerves, Arch. Phys. Med. **32**:71-83, 1951.

64. Busnel, René-Guy; Gliorijevic, J.; Chauchard, P., and Mazoué, H.: Contribution a l'etude des effets et des mechanismes d'action des ultrasons sur le systeme neuro-musculaire, Ultraschall in Med. **6**:1-25, 1953.

65. Fry, W. J.; Tucker, D.; Fry, F. J., and Wulff, V. J.: Physical Factors Involved in Ultrasonically Induced Changes in Living Systems: II. Amplitude Duration Relations and the Effect of Hydrostatic Pressure for Nerve Tissue, J. Acoust. Soc. Am. **23**:364-368, 1951.

66. Woeber, K.: Über das Auftreten von Schädigungen am Zentralnervensystem der Ratte durch Ultraschallwellen, Strahlentherapie **79**:643-652, 1949.

67. Carlin, B.: Ultrasonics, New York, McGraw-Hill Book Company, Inc., 1949.

68. Pohlman, R.: Die Ultraschalltherapie, Bern, Hans Huber, 1951.

69. Iobst, C. W., and Forster, F. M.: Electroencephalographic Foci in Temporal Lobes, Neurology **1**:309-317, 1951.

70. Howarth, J. C., and Gardner, W. J.: Transorbital Leukotomy for the Pain of Malignant Disease, Cleveland Clin. Quart. **19**:140-143, 1952.

ULCERATION AND MALACIA OF THE UPPER ALIMENTARY TRACT IN NEUROLOGIC DISORDERS

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CUSHING [1] in 1931 offered convincing evidence for the revival of once-discarded theories of the neurogenic origin of peptic ulcer. He directed attention to the "interbrain" (diencephalon) as a parasympathetic center. "From this center, apparently tuberal in situation, fibre tracts pass backward to relay with the cranial-autonomic stations of the midbrain and medulla, of which the vagal nucleus is by far the most important because of its influence upon the lungs, heart and upper alimentary canal." Concern over the death, with acute gastrointestinal symptoms, of three patients who had undergone craniotomy for tumor in the posterior cranial fossa caused him to seek an explanation for the postmortem findings common to all, hemorrhagic necrosis with perforation of the esophagus or stomach. More cases with a similar outcome were analyzed. Experimental and pharmacologic evidence was introduced to document findings of medullary or third ventricular compression, intraventricular tumor, cerebral edema, or less well-defined conditions. These phenomena were observed in a total of 11 cases which Cushing used to support a thesis that a "parasympathetic center" lay in the diencephalon. It was admitted that a differentiation could not be made between parasympathetic (diencephalic-vagal) overactivity with inactivity of the normal sympathetic impulses, and the reverse. It was also presumed that gastrointestinal vasoconstriction, a sympathetic response, was present to facilitate ulceration.

Since the reawakening of interest in the problem, many studies have appeared to support the concept of "Cushing's ulcer," a now well-known postoperative complication. Opinions have varied widely about the nature and location of the diencephalic mechanism. Little attention has been given to the occurrence of upper alimentary tract disorders in chronic neurologic disorders not eventuated by intracranial surgery. It is the purpose of this work to present six such cases and to compare them with others gathered from the literature.* This study affords reaffirmation of the clinical significance of the association between the central nervous system and the alimentary tract. Furthermore, a rationale is offered for a modification of the Cushing concept, superimposing upon the diencephalon a "higher" cortical control for which there is

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* References 2 through 9. Donovan, E. J., and Santulli, T. V.: Personal communication to the authors.

now both experimental and clinical evidence. The possibility that the diencephalon may be by-passed entirely in an autonomic effector system is also considered, this theory offering an explanation for those cases in which disorder of the neurologic and gastrointestinal systems are combined, but wherein the hypothalamus has no demonstrable abnormality.

REVIEW OF LITERATURE

The work of Cushing was a cornerstone in the investigation of the diencephalon, and workers thereafter have pursued two avenues of approach.

1. *The Hypothalamus as an Effector in the Autonomic Peripheral System.*—Watts and Fulton [10] in 1935 introduced evidence that the hypothalamic control of the gastrointestinal activity resulting in ulceration was a phenomenon of sympathetic release or irritation. This was based upon the experiments in which a transcallosal or subtemporal approach to the hypothalamus was used to produce a focal lesion, usually anteriorly placed. It is notable that several animals with such lesions had, however, no gastrointestinal abnormality demonstrated at necropsy. There was also Keller [11] in 1936, who observed gastrointestinal lesions after the production of hypothalamic damage in the dog, but he was unsure of the specificity of the relationship because production of the "primary" cerebral lesion was necessarily accompanied by regional surgical trauma and resultant intraventricular debris. This criticism is applicable to all similar efforts. In 1940 Magoun [12] demonstrated descending pathways from the hypothalamus into the pons and spinal cord. That same year Sheehan [13] summarized the experimental data relating to the hypothalamus and the gastrointestinal tract, correlating in part the Cushing thesis and the evidence of Watts and Fulton. He concluded that the anterior hypothalamus, as defined by Rioch and co-workers,[14] was largely "parasympathetic" and the posterior portion "sympathetic" in the regulation of the gastrointestinal activity. It was not concluded whether "excitation" or "inhibition" produced gastrointestinal lesions.

In 1939 Penner and Bernheim [15] reviewed the reported cases of necropsy findings of acute upper alimentary tract ulceration in patients with neurologic and nonneurologic disease and came to the conclusion that such lesions were produced by the vasomotor mechanisms that constitute the response to "shock." These authors observed that "shock" was a commonplace phenomenon in postoperative patients and in those with vascular accidents, massive infections, and other medical catastrophes.

Later, Boles and Riggs [16] presented a series of cases to implicate overactivity of the sympathetic vasoconstrictors in the production of acute gastric ulcers. They reported the incidence of the acute gastric ulceration associated with primary intracerebral disease in patients without organic cardiovascular disease. In these cases, there was either tumor causing generalized increase in intracranial pressure or a more focal process causing interruption of the "central vegetative pathways," and in neither instance, destruction of the hypothalamic nuclear structures. In each case there was observed evidence of "chronic degenerative changes" in the deeper layers of the stomach and similar changes in the remaining viscera, dependent upon "chronic stasis" in the visceral circulatory beds. The conclusion was reached that gastric ulceration under these circumstances was a manifestation of subclinical generalized circulatory insufficiency. This state was said to arise from cerebral stimulation producing prolonged visceral vasoconstriction; such stimulation arose because of increased intracranial pressure associated with tumor or from lesions

focally affecting the vegetative pathways. In cases with primary nonintracranial disease, it was found that of the patients with acute gastric ulcers, 82% also had increased intracranial pressure or changes in the function of the vegetative pathways. These latter conditions were thought to arise from the effects of circulatory insufficiency on the cerebrum. It was noted that ulceration was four times as frequent in cases with such secondary central phenomenon.

French and associates [9] have postulated from clinical and experimental observations that "brain lesions disrupting the balance of visceral function centrally mediated" result in an imbalanced autonomic system. Coincidental with severe stress of injury, illness, or operation, this imbalance is responsible for the formation of gastrointestinal lesions. They contended that hemorrhages arose predominantly as a result of lesions in the anterior hypothalamus (allowing sympathetic overaction) and that erosions occurred after lesions in the posterior hypothalamus, implying that parasympathetic activity was uncontrolled. It was further shown that atropinized animals with lesions of the posterior hypothalamus failed to develop gastrointestinal pathologic changes (i. e., parasympathetic overaction was blocked), and that tetraethylammonium (Etamon) chloride, a general autonomic-blocking agent, similarly prevented such changes in animals with anterior hypothalamic lesions.

2. Cortical Control of Activity Presumed Centered in the Hypothalamus.—Clinical and research interest took a second direction when Dragstedt † investigated the effect of vagal section in the cephalic phase of gastrointestinal activity. Using clinical and surgical experimental data, he showed that parasympathetic action, or sympathetic inaction, is requisite to general excess of motility and secretion in the lower esophagus, the stomach, and duodenum, which, in turn, facilitates ulceration. The problem of clinical peptic ulcer is so often associated with psychosomatic, thereby presumably "supradiencephalic," mechanisms that new interest was focused upon the possible cortical control of activity presumed centered in the hypothalamus.

It will be recalled that Watts and Fulton,[19] in 1934, demonstrated in monkeys a distinct autonomic representation for the gastrointestinal tract in the premotor cortex. Mettler and associates [20] confirmed this evidence in dogs subjected to selective cortical ablation and concluded that the more acute of such lesions was associated with hyperemia and congestion of the alimentary tract, while the more chronic lesions accompanied frank ulceration. In 1947 Ward and McCulloch,[21] using physiologic neuronographic methods, described projections of the frontal lobe to the hypothalamus in monkeys. Area 6*A* was found to project to the mammillary nuclei and to the lateral and posterior portions of the hypothalamus; the frontal lobe projected to the supraoptic and paraventricular nuclei, and its orbital surface projected to the posterior portion of the hypothalamus as well. In 1948 Ward,[22] using monkeys, demonstrated in Marchi preparations a projection of the anterior cingular gyrus (Area 24) to the pons which circumvented the hypothalamus but exerted a powerful cortical suppressor activity as an autonomic effector. Babkin and Speakman [23] in 1950 confirmed the phenomenon of cortical inhibition of gastric motility in dogs, implicating the anterior cingular gyrus and the insular-orbital surfaces of the frontal lobe. Studying pyloric and gastric motility in relation to these areas in the canine cortex (postulating the insular-orbital area as analogous to isle of Reil in man), Babkin and Kite ‡ con-

† References 17 and 18.

‡ References 24 and 25.

cluded that the hypothalamus acted as a way station above the dorsal motor nuclei of the vagi to regulate gastrointestinal motility. Cortical control, while present, did not necessarily act through the hypothalamus. It remained for Babkin [26] to summarize the problem of the role of the hypothalamus in gastrointestinal activity by moderating the Cushing concept. He concluded it was doubtful that hyperactivity of the parasympathetic and bulbar centers is due to the lack of inhibition from a hypothalamic center. "It is more in agreement with the facts to admit the loss by gastric parasympathetic centers of the cortical control which exerts a moderating influence upon them."

The contention that the hypothalamus is not necessarily operative in gastrointestinal function is supported by the observations of Wall and Davis,[27] in 1951, that there were three cortical systems affecting autonomic activity (blood pressure), two of which do not involve the mediation of the hypothalamus but do involve the medullary vagal centers. These systems arose from the sensorimotor cortex and the temporal lobe. In 1952 Jasper and associates [28] described corticofugal projections to the brain stem which traversed the thalamus, the subthalamus, and the substantia nigra, but not the hypothalamus.

It is well known that gastrointestinal ulceration need not occur in the presence of hypothalamic or more widespread intracranial disorder. Opper and Zimmerman [4] reported two such cases in their series to emphasize the phenomenon. Rather negative experimental evidence is given by Hess,[29] who observed the results of thalamic, subthalamic, and hypothalamic lesions in over 400 cats. He did not comment upon a single gastrointestinal finding. Watts and Fulton [10] made somewhat similar observations. Brouwer [30] did not list any gastrointestinal disorders among his myriad of findings in patients with proved hypothalamic lesions. In our necropsy records there are numerous cases of hypothalamic involvement in neurologic diseases which were not accompanied by gastrointestinal disorder.

Three concepts have now been established:

(*a*) There is an anatomic pathway to mediate hypothalamic-vagal autonomic effects on the gastrointestinal tract.

(*b*) There is some evidence to suggest that such hypothalamic control may result in ulceration because of excessive sympathetic activity, producing "visceral circulatory stasis," or resulting from shock. There is also evidence that hemorrhage is related to sympathetic nervous system activity and that ulceration is related to the parasympathetic system.

(*c*) There is recent experimental and clinical reason to suspect that the hypothalamic centers are not solely involved in the production of gastrointestinal pathologic changes, since cortical or subcortical centers have been elucidated which may have an effect upon hypothalamic or vagal centers.

REPORT OF CASES

Six previously unreported cases of combined neurologic and gastrointestinal disorder are presented. In each case irrelevant clinical and laboratory data have been omitted.

CASE 1.—A. J., a woman aged 36, entered Montefiore Hospital in 1951, with a six-year history of progressive weakness of the legs. The significant findings in the nervous system were past pointing and ataxia of all extremities, spastic paraparesis, and a bilateral Babinski sign.

A cervical myelogram was interpreted as normal, and a diagnosis of multiple sclerosis was postulated. For the next five months the patient's course was unremarkable. In August, 1951, she suffered the onset of unheralded acute abdominal symptoms and signs suggesting a ruptured viscus. Laparotomy revealed early peritonitis, with gas and fluid in the abdominal cavity and a perforation high on the posterior wall of the stomach. The mucosa surrounding this gaping hole was edematous and slightly indurated, but there was no evidence of chronic ulceration. Closure was accomplished with silk sutures, but her postoperative course was stormy. She died 48 hours later in shock, with hyperthermia of 107 F.

Necropsy (performed seven hours post mortem by Dr. A. Ehrlich).—There was reaccumulation of fluid and air in the abdominal cavity and fresh perforation at the site of the earlier closure, with extensive gastromalacia giving a thin and friable character to the organ (Fig. 1). Microscopic examination revealed early peritonitis as well as gastromalacia with ulceration. There was no generalized visceral congestion.

The cerebral hemispheres were mildly atrophic. Section of the brain disclosed numerous discolored plaques in the subcortex and at corticomedullary junctions. Plaques were seen in the corpus callosum, septum pellucidum, internal capsule, periventricular gray matter, posterior

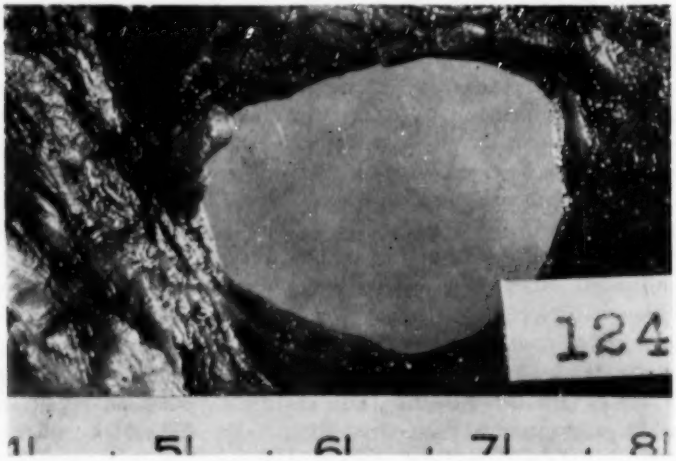

Fig. 1 (Case 1).—Photograph of the recurrent gastric perforation. Note the smooth, atrophic mucosa. The scale markings below are in centimeters.

hypothalamic nuclei, calcarine cortex, and periventricular and basilar portion of pons, cerebellum, and spinal cord.

Microscopic examination revealed scattered plaques of demyelination in the described regions. They were of different size and age and were typical of multiple sclerosis.

Comment.—There was no history suggestive of previous alimentary tract disorder in this woman. An effort was made to repair the perforation in a stomach with extensive malacia, and the patient died soon thereafter with hyperthermia and a fresh perforation.

Case 2.—E. G., a woman aged 33, entered Montefiore Hospital in September, 1951, to undergo right lower lobectomy for pulmonary tuberculosis. Examination revealed findings consistent with her pulmonary condition. On Oct. 4, after heavy premedication because of agitation, anesthesia was begun, using a 50 : 50 cyclopropane-oxygen mixture. Within four minutes apnea occurred and persisted for at least another four minutes despite remedial measures. Unaided respiration was not established for an hour. It was the anesthetist's opinion that blood pressure and pulse were maintained throughout the entire episode and, indeed, were seen to

become slightly augmented. The patient remained in deep coma with occasional convulsive movements of the left arm. On the 15th postanesthetic day there was an elevation of temperature to 107 F., which fell rapidly with alcohol sponging and hydration. She was afebrile at death, three days later.

Necropsy (performed 11 hours post mortem by Dr. H. Laufer).—In addition to the findings of pulmonary tuberculosis there was extensive gastromalacia, causing the stomach to appear smooth, pale, and markedly thin. There were two ulcerations in the duodenum. The first ulcer, 1 cm. in diameter, was perforated; the second, 2 cm., was superficial. Microscopic examination of the stomach disclosed the muscularis to be edematous and thin. The mucosa and submucosa were completely necrotic, so that the normal architecture was destroyed. The perforated ulcer was acute, with underlying necrosis and a slight leucocytic reaction at the base. The second had a more profuse reaction in the submucosal base. There was no evidence of generalized visceral congestion.

Macroscopic examination of the brain revealed gray matter with a brown discolored line in the third and fourth layers, or in the outer three layers. There were scattered petechiae in the walls of the third ventricle.

On microscopic examination the white matter was found well preserved, but all layers of the cortex were altered, displaying changes ranging from increased satellitosis of ganglion cells to complete destruction of the third and fourth layers with active gliosis. The cornua ammonis revealed only minimal cell loss. There were infarcts in the anterior thalamic nuclei, posterior portion of the hypothalamus, and inferior geniculate bodies, and cell loss with neuronophagia in the spinal cord and cerebellum. The diagnosis was widespread loss of neurons and infarction secondary to anoxia.

Comment.—The cortical changes secondary to anoxia are well demonstrated in this case, although the sparing of the cornua ammonis and the involvement of the spinal cord are somewhat unusual. In this instance acute ulceration accompanied the perforation. There was no clinical recognition of these findings in this comatose patient.

Case 3.—W. McAl., a man aged 73, entered Montefiore Hospital for the second time in June, 1952, for elective closure of colostomy, which had been undertaken nine months previously for diverticulitis. Gradually increasing weakness of his left extremities had been noted for two months prior to his reentry. The principal findings were arterial hypertension of 190/100, a functioning colostomy, and a left hemiparesis. There was a suggestion of visual field constriction on the left. An electroencephalogram disclosed bilateral diffuse 6 to 8 per second activity without focality, interpreted as a slight deviation from the electrical normal. On June 26, 1952, the colostomy was closed, using regional anesthesia. The patient did well for the next 36 hours. Confusion, drowsiness, increasing hemiplegia, and eventual coma ensued. A neurologic consultant having suggested the possibility of slow closure of the right middle cerebral artery, right carotid angiography was undertaken. There was no filling in the cervical portion of the right internal carotid artery. The patient died 72 hours after operation, with a terminal temperature of 103 F.

Necropsy (performed four hours post mortem by Dr. A. Johnston).—In addition to healed diverticulitis of the colon and generalized arteriosclerosis, there was an almost complete occlusion of the right internal carotid artery by a sclerotic plaque, with a thrombus extending into the intracerebral branches. The cardia and proximal portions of the stomach were malacic, with complete disappearance of the mucosa, revealing a paper-thin submucosa and muscularis (Fig. 2) and a gaping perforation 3 cm. in diameter. Microscopic examination revealed no cellular reaction at the perforation and complete obliteration of the normal architecture of the gastric wall (Fig. 3). There was no evidence of generalized visceral congestion.

Macroscopic examination of the brain revealed massive infarction of the right cerebral hemisphere accompanying thrombosis of the internal carotid artery extending into the finer radicals of the middle cerebral artery. The right centrum ovale, corpus callosum, basal ganglions, and hypothalamus were infarcted, and the third ventricle was bowed to the left as a result of the swelling on the right. Multiple fresh hemorrhages were scattered in both the

tegmental and the basilar portion of the pons. There was an ancient malacic focus in the left occipital lobe and several minute infarcts of different ages scattered throughout the cortex, subcortex, and basal ganglions of the left hemisphere.

Microscopic examination disclosed that the gray matter in the freshly infarcted area was diffusely necrobiotic, with congestion and dilatation of the blood vessels. Fresh infarction was apparent in the right side of the hypothalamus, accompanied by a leucocytic exudation. The malacic focus in the occipital region was lined with pigment-laden macrophages and was obvi-

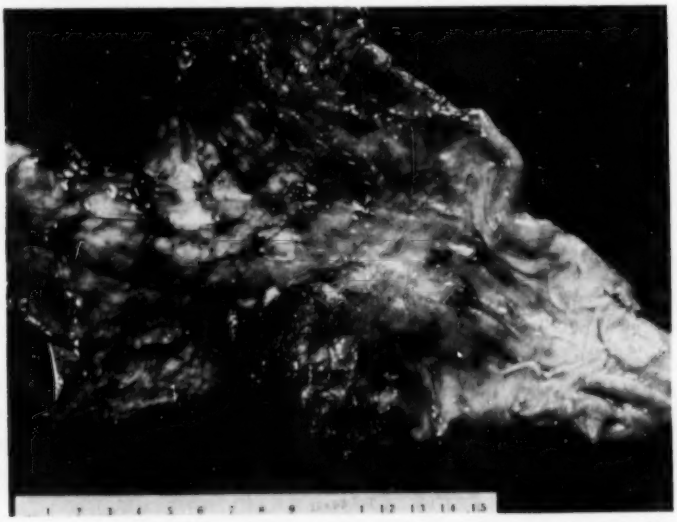

Fig. 2 (Case 3).—Photograph of the mucosal surface of the stomach. The blood-stained malacic portion is sharply delimited from the normal prepyloric region.

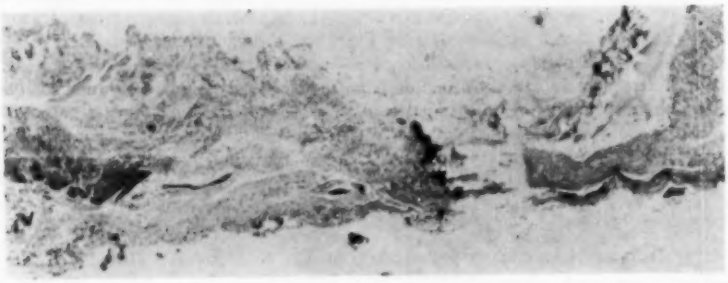

Fig. 3 (Case 3).—Photomicrograph of the wall of the stomach. Severe gastromalacia has resulted in complete obliteration of the architecture. Hematoxylin and eosin technique, × 23.

ously old. The pontine hemorrhages were perivascular and fresh. The minute infarcts in the left cerebral hemisphere were of different ages. The diagnoses were bilateral cerebral and pontine hemorrhages and infarcts secondary to arteriosclerosis and thrombosis of the internal carotid artery.

Comment.—It is not common to find such a vascular process responsible for a protracted and progressive neurologic deficit. The regional block (T8 to T12) anesthesia and operation were probably unrelated to the fresh thrombosis of the carotid artery. The latter might be dated to the sudden progress of symptoms 36

hours before death. Because the perforation was without peritoneal reaction, it is considered agonal, but the time interval is too short to attribute the circumscribed malacia to postmortem autolysis.

CASE 4.—K. R., a man aged 36, entered Montefiore Hospital in June, 1953. A pigmented lesion had been removed from his back in 1945, and he had received x-ray therapy to the operative site. In April, 1953, after a month's duration of headache, nausea, and vomiting, he had been admitted to another hospital, where the findings consisted of many pigmented nodules in the skin, left-sided hyperreflexia, decalcification of the posterior clinoids, and an abnormal focus in the electroencephalogram. Bilateral carotid angiography revealed a mass in the right frontal lobe, which was revealed by craniotomy to be metastatic melanoma. Roentgen therapy was given and the patient transferred to this hospital for further treatment. Here the signs and symptoms were much the same, in addition to a bulging decompression. There was a moderate electrolyte imbalance and dehydration secondary to pernicious vomiting. While these conditions were being corrected, efforts were made at decompression by ventriculostomy with polyethylene tubing and repeated lumbar punctures. He died within a month of admission. There was terminal hyperthermia of 106 F.

Necropsy (performed three hours post mortem by Dr. J. Berner).—There were many blue nevi in the skin, and metastatic tumor nodules were found in the gastrointestinal tract, gall bladder, liver, lymph nodes, and lungs. There was a collection of dark fluid in both pleural spaces, with necrosis and digestion of the lower portion of the mediastinum. This process arose from a perforation of the lower part of the esophagus with nearby ulceration. There were also ulcerative gastric and duodenal lesions overlying metastatic tumor nodules, but there was no evidence of malignancy in the esophageal lesions. Microscopic examination confirmed this latter impression. The esophageal ulcerations had a moderate leucocytic reaction at the base. There was no evidence of generalized visceral congestion.

There was a large herniation of the brain through the operative defect overlying a recurrent tumor nodule in the right frontal lobe There was no other evidence of cerebral swelling. The right basal ganglion, the periventricular gray matter, and left putamen were studded with tumor emboli. The basal leptomeninges were darkly pigmented.

Microscopic examination disclosed metastatic melanoma in the right frontal lobe, many other areas of the cortex and subcortex, the basal ganglions, the thalami, the hypothalamus, the wall of the third and fourth ventricles, the leptomeninges of the base, the medulla, and the cerebellum.

Comment.—The clinical impression of increased intracranial pressure was not borne out by the necropsy to the degree anticipated. In view of the neoplastic involvement of the hypothalamus and related structures, one might assume that the gastrointestinal symptoms arose from such neoplastic infiltrations rather than from the effect of increased intracranial pressure. The metastases to the alimentary tract itself might also have played a role. There is no doubt that the ulceration and perforation were present ante mortem but were not recognized clinically.

CASE 5.—L. S., a man aged 47, entered Montefiore Hospital in 1914. For the previous five years he had noted remissive double vision, staggering, and tremor. Examination revealed bilateral nystagmus, right facial weakness of central type, ataxia, dysarthria, and intention tremor. The diagnosis of multiple sclerosis was made. Over the next five years he gradually developed spastic quadriparesis and severe ataxia. His neurologic condition then remained static. In 1922 he developed postprandial epigastric pain and tenderness, relieved by induced vomiting. X-ray studies showed only delayed gastric emptying. Chronic distress was relieved six months later, when a strict Sippy diet was instituted. Repeated x-ray studies were negative for ulcer. It had been the hypothesis of the neurologic examiner that perhaps the gastrointestinal symptoms were of "central" origin, but this opinion was withdrawn when the response to medical management became apparent. For the next six years the patient did well except for dietary indiscretions which resulted in pain and vomiting. His neurologic condition remained unaltered. In April, 1928, at age 61, the patient died suddenly within 10 minutes following the onset of "collapse."

Necropsy (performed three hours post mortem by Drs. M. Deutsch and D. Perla).—The esophagus was normal, but the stomach contained two blood clots. Just below the pylorus the duodenum presented a deep ulcer crater, 1 cm. in diameter, with an eroded thrombosed vessel at the base. The entire bowel was filled with partly clotted blood. There were two acute ulcerations in the esophagus, with a moderate leucocytic reaction at the bases.

In the brain, internal hydrocephalus without obstruction was present. A description of the cut surfaces of the brain is not available in the hospital records.

The microscopic examination revealed scattered demyelinated zones in both hemispheres, through the corona radiata, internal capsules, thalami, hypothalamus, and subcortex. A large plaque was present in the dorsal portion of the medulla. The diagnosis was multiple sclerosis.

Comment.—The relationship of the early ulcer symptoms to the disease found in the brain must be speculative, and no clear-cut inference may be drawn from the association. None of the plaques appeared fresh, and the neurologic clinical status had been unchanging. Although x-ray evidence was wanting, peptic ulcer was probably present for six years before death. The question of its neurogenic origin must remain unanswered. The final event appears to have been massive bleeding from the chronic ulcer, but the fresh esophageal ulcerations are definitely antemortem phenomena and bespeak some terminal "hyperstimulation" of the gastrointestinal tract. It cannot be ascertained whether these lesions are related to an "ulcer diathesis" responsible for the long-standing ulcer, and not necessarily related to neurologic disorder, or whether they are of "central" etiology. This case is included because it may represent a bridge between the neurogenic and the "nonspecific" origins for gastrointestinal ulceration.

Case 6.—S. O., a 68-year-old man, was admitted to Montefiore Hospital on Sept. 3, 1953, with a diagnosis of subarachnoid hemorrhage and a possible subdural hematoma. Two days before he had fallen when a chair gave way and struck the right side of his head. A physician, called to examine him, found "nothing wrong." The patient then retired for the evening but awakened the next morning to find that he was unable to speak, could not move his left side well, and indicated with gestures that he had a headache. By evening he was unresponsive to all but painful stimuli. Past history obtained from the family included an episode of coronary thrombosis in 1945 and arterial hypertension, diagnosed in 1949. The family recalled that for the past two years he had complained of "numbness of the entire left side" and that there had been gradual personality deterioration. Nine months prior to admission there had been transient weakness of the left side of his face.

Examination revealed blood pressure of 190/110, deep coma with movement of the right side only (when painfully stimulated), deviation of the right eye to the left, left facial weakness and hemiplegia, left Babinski sign, and marked neck rigidity. The most likely diagnoses were considered to be a right intracerebral hemorrhage or subdural hematoma. Under local anesthesia, burr holes were placed in the right frontotemporal and the right occipitotemporal region. Exploration was unrevealing, and there was no increase in pressure. Ventricular puncture was productive of clear, colorless fluid. Needling to discover an intracerebral hematoma was unproductive. Immediately thereafter, lumbar puncture produced normal-appearing fluid under no increase in pressure. The protein content of this fluid was 56 mg., the sugar, 105 mg., and the chlorides, 132 mg. per 100 cc. The condition of the patient did not change. Ventriculography was then performed, revealing a normal ventricular system. On this day there was leucocytosis with a count of 20,800 per cubic millimeter and 70% neutrophiles. Hydration and correction of electrolytes was undertaken. The next day, lumbar puncture disclosed cloudy fluid with 1,320 white blood cells per cubic millimeter and a sugar level of 108 mg. per 100 cc. Organisms were not seen on smear. Efforts to culture an organism were unsuccessful. During this time the temperature ranged up to 105 F. in spite of the use of antibiotics. The blood urea nitrogen rose to 45 mg. per 100 cc. After two subsequent days with relatively normal temperatures and slight improvement in sensorium, aspiration and pneumonitis occurred, with temperature spikes to 105 F. and 107 F. The patient died quietly on Sept. 11, eight days after admission.

Necropsy (performed 16 hours post mortem by D. I. Almenoff).—The general examination revealed extensive arteriosclerosis, with an old healed myocardial infarct. In the duodenum there were three bloody superficial ulcerations, and fresh blood in the small and large intestines. Microscopic examination revealed focal malacia and necrosis of all layers of the fundal portion of the stomach. The duodenal ulcerations were superficial and contained blood pigment at the bases.

There was no gross evidence of meningitis in the brain. The right cerebral hemisphere was swollen, and there was anemic infarction of the basal surfaces of the right frontal and occipital lobes. A fresh thrombus was seen in the cavernous sinus portion of the right internal carotid artery. The right posterior communicating artery was sclerotic and occluded by a fresh thrombus. Section of the brain revealed infarction and softening of the right temporal lobe, with extension into the basal ganglions and internal capsule. There was also an old malacic cyst in the right side of the pons.

Microscopic examination also failed to reveal evidence of meningitis. There was almost complete obliteration of the right internal carotid and posterior communicating arteries by fresh antemortem thrombi, an anemic infarct in the right parietal lobe near the site of needling, and the massive infarct seen grossly. Confirmation was made of the pontine infarct, transecting the ascending sensory pathways. In addition, there were small, old and recent, foci of malacia on both sides of the thalamus and hypothalamus, and the cortex and subcortex. The diagnosis was multiple cerebral and pontine infarcts, secondary to arteriosclerotic thrombosis.

Comment.—The lesion in the pons was old and was correlated with the two-year history of left-sided numbness. As in Case 3, thrombosis of the internal carotid artery was associated with ulceration, widespread malacia, and hemorrhage in the stomach.

GENERAL COMMENT

An accumulation of 44 cases with combined neurologic and gastrointestinal disorder, confirmed by complete necropsy examination, affords comment upon the concept earlier presented. Six of the cases are those detailed above; the remainder are selected from the literature.§ The bases for selection were that there be complete necropsy reports and that there be as little question as possible that the gastrointestinal changes were genuinely ante mortem. The original Cushing series is not included because there were no reports of the findings in the brain upon microscopic examination. Other reports are omitted in whole or in part for the same reason. Evidence of the antemortem nature of the alimentary tract changes was obtained from the history, the nature of the systemic response to these changes, or the peculiarities of the lesions themselves.

The 38 cases from the literature included patients of both sexes, ranging in age from newborn to 88 years. The 38 primary diagnoses are tabulated as follows:

Suppurative meningitis, with or without brain abscess	9
"Vascular accidents"	8
Tumor, primary or metastatic, preoperative and postoperative	7
Head injury and birth trauma	6
Viral infections, encephalitis, and poliomyelitis	4
Asphyxia	2
Neonatal convulsions, malnutrition	1
Gunshot wound	1

To this number are added the six cases detailed in this report:

Multiple sclerosis	2
Cerebrovascular thrombosis	2
Metastatic melanoma	1
Asphyxia	1

In all cases, review was made to ascertain the neurologic sites involved, primarily or secondarily, which represented regions from which gastrointestinal regulation has

§ References 2 through 9. Donovan, E. J., and Santulli, T. V.: Personal communication to authors.

been said to arise. These regions are the cortex, subcortex, hypothalamus, pons, and medulla. The meninges were also surveyed because of their close relationship to cortical physiologic activity.

The following observations are made:

1. No case was found to have evidence of the "visceral circulatory stasis" which Boles and Riggs contended was the underlying condition in the production of acute gastric ulcer of neurogenic origin. Little can be derived here for verification of their conclusions or the inference by them that sympathetic activity (vasoconstriction) was significant in the production of such gastric ulceration. Neither does this observation validate the Cushing corollary of focal vasoconstriction at the site of incipient ulceration.

2. The experimental evidence in cats [9] that hemorrhages and erosion are specifically related to sympathetic and parasympathetic functions, respectively, cannot be further elucidated. The clinical data here analyzed do not contain instances of lesions so precisely localized as in experimental situations (remembering that no "lesion" can be created without undesirable trauma, etc.). In addition, the problem of differing responses in various species has not been answered.

3. Some of the cases were of clinical interest because of antemortem symptoms of alimentary tract disorder. In seven of the cases there was at least terminal hematemesis, and in three cases there were sufficient symptoms to cause clinical concern. The first of the three patients (Case 5),[2] with a tumor of the corpus callosum, required transfusion after hematemesis a week before death and bled once again, terminally; the second (Case 4),[9] a patient with hypertension and peptic ulcer, had repeated hematemesis before death. Necropsy disclosed multiple gastric and duodenal ulcers and esophageal perforation; the third (our Case 1) underwent laparotomy for acute abdominal signs arising from perforation of the stomach. Surgical closure was fruitless in the presence of severe gastromalacia, but the patient lived two more days before this fact was verified at necropsy. In most cases terminal hyperthermia seemed to coincide with the development of the alimentary tract lesions, or the clinical manifestations of these lesions. It will be noted also that alimentary tract lesions can develop in patients with various types of neurologic disorders, not necessarily postoperative patients with brain tumors.

4. In the cases surveyed there was no case with restriction of the neurologic disease to the hypothalamus alone. In all, there was associated pathologic change in adjacent or distant regions of the brain. In one case,[6] which at first appeared to have solely a hypothalamic lesion (an infant with a tumor of the tuber cinereum, duodenal ulceration, and gastromalacia), there was also reported "meningitis" at necropsy. Similar observations were made upon postoperative brain tumor cases. Multiple metastases, widespread changes associated with increased intracranial pressure, bilateral lesions secondary to cerebral arteriosclerosis, etc., were found in all cases, in addition to the primary lesions. It was concluded that sites of major disease processes were as follows:

	No. of Cases
Meninges	25
Cortex	37
Subcortex	28
Hypothalamus	30
Pons	16
Medulla	9

Thus it will be seen that there is no single site common to all 44 cases.

It is of interest that the hypothalamus was significantly involved in only 30 cases. In many of the remainder there were changes of the least apparent order of physiologic and anatomic magnitude, but in at least five‖ there was no pathologic change whatever, despite careful search. Although the cases cited by Cushing are not surveyed, the nature of the primary disorder in each instance was such that the lesions in no case could be confined solely to the diencephalon and grossly involved the meninges, cortices, etc.

These latter observations raise the question whether a "higher" center might be enlisted in the neurologic-alimentary axis, and whether it is not possible to by-pass the hypothalamus entirely, upon occasion. As we have seen, there is good experimental evidence to support such a concept. Accepting the neurologic mechanism of "higher center (cortical-subcortical)→hypothalamus→vagal nuclei," or of "higher center→vagal nuclei," alters the Cushing concept, which did not admit of influence higher than the hypothalamus as a primary effector, and in part answers his query about the nature of the hypothalamic-vagal influence. In this modified concept the cortex moderates or "damps" the lower centers, and with the latter allowed unbridled activity because cortical centers or pathways are not functioning, an excessive parasympathetic effect is wreaked upon the viscera. This excess becomes the modus operandi of ulceration and malacia. No verification can be offered of the parts played in the mechanism of the formation of these lesions in man by either sympathetic activity alone or specific anatomic portions of the hypothalamus. The widespread intracranial lesions, and in some instances the absence of hypothalamic disorder, do not permit such observations. The use of autonomic blocking agents in the treatment of the gastrointestinal disturbances is strongly suggested by the work of French and associates.[9]

Last, it must be stated that despite the strongest inferences that can be drawn from the association of neurologic and gastrointestinal disorders, no physical proof of their direct relationship has yet been established.

SUMMARY AND CONCLUSIONS

There are presented six cases of chronic neurologic disease (multiple sclerosis, asphyxia, cerebral infarction, and metastatic tumor) associated with antemortem ulceration or malacia of the upper alimentary tract.

Literature upon this combination of disorders has been reviewed, and 38 similar cases have been gathered. The entire collection is analyzed regarding general necropsy findings and designation of the sites of neurologic disease, with particular reference to areas known to be implicated experimentally in an autonomic gastrointestinal effector system. There was no case observed to have general visceral congestion or circulatory stasis. This would not support earlier theses regarding the development of acute gastric ulceration in neurologic disorders. Despite the universal finding of gastrointestinal disorder, not all patients had anatomic lesions demonstrable in the hypothalamus; yet all had such derangement in meningocortical or subcortical areas. This observation is examined in the light of reports of experiments establishing "higher" projections upon known centers for gastrointestinal regulation in the hypothalamus and medulla.

‖ References 4 and 7.

It may be concluded that cortical or "supradiencephalic" centers have a moderating influence upon the diencephalic-vagal centers, and that failure of this influence is productive of an uncontrolled activity of either of the latter centers, which results in ulceration or malacia of the upper alimentary tract. Emphasis is given the concept that the "Cushing ulcer" and related phenomena are not restricted to the postoperative craniotomy patient, nor are such phenomena only of postmortem significance. Occasional patients with chronic neurologic disorders may present clinical problems of ulceration and malacia in the alimentary tract.

REFERENCES

1. Cushing, H.: Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System: IV. Peptic Ulcer and the Interbrain, Springfield, Ill., Charles C Thomas, Publisher, 1932.

2. Masten, M. G., and Bunts, R. C.: Neurogenic Erosions and Perforations of the Stomach and Esophagus in Cerebral Lesions, Arch. Int. Med. **54**:916-930, 1934.

3. Craig, W. S.: Duodenal Ulcers in the Newborn, Arch. Dis. Childhood **9**:57-64, 1934.

4. Opper, L., and Zimmerman, H. M.: Ulcers of the Digestive Tract in Association with Cerebral Lesions, Yale J. Biol. & Med. **11**:49-84, 1938.

5. Donovan, E. J., and Santulli, T. V.: Gastric and Duodenal Ulcers in Infancy and Childhood, Am. J. Dis. Child. **69**:176-179, 1945.

6. Mossberger, J. I.: Perforated Duodenal Ulcer and Neoplasm of the Tuber Cinereum in the Newborn, J. Neuropath. & Exper. Neurol. **6**:391-400, 1947.

7. Heyde, E. C., and Robinson, S.: Acute Peptic Ulceration Accompanying Bulbar Poliomyelitis: Report of 2 Cases, Gastroenterology **11**:519-522, 1948.

8. Wyatt, J. P., and Khoo, P. N.: Ulcers of the Upper Part of the Gastrointestinal Tract Associated with Acute Damage of the Brain, Arch. Path. **47**:110-118, 1949.

9. French, J. D.; Porter, R. W.; von Amerongen, F. K., and Raney, R. B.: Gastrointestinal Hemorrhage and Ulceration Associated with Intracranial Lesions, Surgery **32**:395-407, 1952.

10. Watts, J. W., and Fulton, J. F.: Effect of Lesions of the Hypothalamus upon the Gastro-Intestinal Tract and Heart of Monkeys, Ann. Surg. **101**:363-372, 1935.

11. Keller, A. D.: Ulceration in the Digestive Tract of the Dog Following Intracranial Procedures, Arch. Path. **21**:127-164, 1936.

12. Magoun, H. W.: Descending Connections from the Hypothalamus, A. Res. Nerv. & Ment. Dis., Proc. (1939) **20**:270-285, 1940.

13. Sheehan, D.: Hypothalamus and Gastro-Intestinal Regulation, A. Res. Nerv. & Ment. Dis., Proc. (1939) **20**:589-616, 1940.

14. Rioch, D. McK.; Wislocki, G. B., and O'Leary, J. L.: Précis of Preoptic, Hypothalamic and Hypophysial Terminology with Atlas, A. Res. Nerv. & Ment. Dis., Proc. (1939) **20**:3-30, 1940.

15. Penner, A., and Bernheim, A. I.: Acute Postoperative Esophageal, Gastric and Duodenal Ulcerations, Arch. Path. **28**:129-140, 1939.

16. Boles, R. S., and Riggs, H. E.: Neurogenic Factors in the Production of Acute Gastric Ulcer, J. A. M. A. **115**:1771-1773, 1940.

17. Dragstedt, L. R.: Pathogenesis of Gastroduodenal Ulcer, Arch. Surg. **44**:438-451, 1942.

18. Dragstedt, L. R.: Section of the Vagus Nerves to the Stomach in the Treatment of Peptic Ulcer, Surg., Gynec. & Obst. **83**:547-549, 1946.

19. Watts, J. W., and Fulton, J. F.: Intussusception: Relation of Cerebral Cortex to Intestinal Motility in the Monkey, New England J. Med. **210**:883-896, 1934.

20. Mettler, F. A.; Spindler, J.; Mettler, C. C., and Combs, J. D.: Disturbances in Gastro-Intestinal Function After Localized Ablations of the Cerebral Cortex, Arch. Surg. **32**:618-623, 1936.

21. Ward, A. A., Jr., and McCulloch, W. S.: Projection of the Frontal Lobe on the Hypothalamus, J. Neurophysiol. **10**:309-314, 1947.

22. Ward, A. A., Jr.: Cingular Gyrus: Area 24, J. Neurophysiol. **11**:13-23, 1948.

23. Babkin, B. P., and Speakman, T. J.: Cortical Inhibition of Gastric Motility, J. Neurophysiol. **13**:55-63, 1950.

24. Babkin, B. P., and Kite, W. C., Jr.: Central and Reflex Regulation of Motility of Pyloric Antrum, J. Neurophysiol. **13**:321-334, 1950.

25. Babkin, B. P., and Kite, W. C., Jr.: Gastric Motor Effects of Acute Removal of Cingulate Gyrus and Section of Brain Stem, J. Neurophysiol. **13**:335-342, 1950.

26. Babkin, B. P.: Cerebral Cortex and Gastric Motility, Edinburgh M. J. **57**:419-430, 1950.

27. Wall, P. D., and Davis, G. D.: Three Cerebral Cortical Systems Affecting Autonomic Function, J. Neurophysiol. **14**:507-517, 1951.

28. Jasper, H.; Ajmone-Marsan, C., and Stoll, J.: Corticofugal Projections in the Brain Stem, A. M. A. Arch. Neurol. & Psychiat. **67**:155-171, 1952.

29. McDonald, D. A.: W. R. Hess: Control of the Autonomic Nervous System by the Hypothalamus, Lancet **1**:627-629, 1951.

30. Brouwer, B.: Positive and Negative Aspects of Hypothalamic Disorders, J. Neurol., Neurosurg. & Psychiat. **13**:16-23, 1950.

BRAIN CHANGES IN PATIENTS WITH EXTENSIVE BODY BURNS

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THERE are approximately 8,000 deaths of burns each year in the United States.[1] With the newer concepts of treatment for burns, an increasing number of patients are kept alive who formerly may have succumbed. Although it is not possible to determine the incidence of brain changes in people with body burns, several cases have been reported. There are, however, so few neuropathological studies that, in order to describe the cerebral changes and their possible clinical implications, we are reporting two cases of patients who suffered extensive burns.

REPORT OF CASES

CASE 1.—A 14-year-old boy suffered third-degree burns of 40% of his body surface in an airplane accident and lived 16 days. He was treated with plasma, whole blood, antibiotics, corticotropin (ACTH), and intravenous fluids. He became irrational on the seventh day, then anuric, and went into stupor; his temperature rose to 104 F., and he died. His brain showed toxic ganglion cell changes, small fresh hemorrhages in the white matter, and focal areas of demyelination.

W. E., NH17453. A 14-year-old white boy was in an airplane accident May 13, 1951, in which he suffered third-degree burns of 40% of his body surface. He was treated at a local hospital with 1,500 cc. of plasma. His blood count at that time was 65% hemoglobin, 4,520,000 red cells, and 8,600 white cells. The next day he was nauseated and vomited, and he was given 2,000 cc. of 5% dextrose in saline. Four days later the white cell count had risen to 14,900, and the hemoglobin had dropped to 54%, with 3,000,000 red cells. On each of the two following days he was given 2 pints (950 cc.) of whole blood. He became slightly irrational, and this state persisted through his hospitalization. The next day jaundice of the skin and sclerae was noticed. At this time the blood urea nitrogen was 10 mg. per 100 cc., the plasma chlorides 500 mg. per 100 cc., and the icteric index 35. The urine was dark amber and was positive for bile. Urinary intake and output were reported as good.

Ten days after his accident the patient was transferred to the Jefferson Medical College Hospital, where he was found to have multiple third-degree burns of the face, hands, and legs. The burns of the face were covered with crusts. The arms and hands were bandaged, and the legs were in plaster casts. The past history was not significant.

Examination revealed an irrational, pale boy, who was constantly nauseated and retching. Examination was greatly limited because of the bandages and casts. The blood pressure on admission was 160/80, temperature (axilla), 100 F., and pulse rate 100. The scalp over the frontal area was lacerated where he had struck his head in the crash. He had conjunctivitis, and the eyelids were lacerated. The sclerae were jaundiced, and there was clotted blood in the nostrils.

The pupils were oval in shape and reacted slowly to light and in accommodation. Nystagmoid movements were seen when the eyes were fixed, but there was no true nystagmus and there was a full range of movement of the eyes. He had good strength in his extremities, with

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no evidence of spasticity. The abdominal and cremasteric reflexes were absent. Laboratory studies revealed a hemoglobin of 65%, 3,300,000 red cells, and 9,200 white cells, of which 49% were segmented and 12% nonsegmented neutrophiles and 39% lymphocytes. Blood urea nitrogen was 3.4 mg. per 100 cc., creatinine 1.0 mg. per 100 cc., and plasma proteins 5.19 mg. per 100 cc. with 3.39 mg. of albumin and 1.8 mg. of globulin. Lumbar puncture revealed an initial pressure of 195 mm. of water, the spinal fluid being yellow in color.

The patient was treated with penicillin, corticotropin, potassium citrate, intravenous fluids, chlortetracycline (Aureomycin), and plasma, but he became anuric and developed periorbital edema. On the 16th day after the accident he went into a stupor, his temperature rose to 104 F., and he died.

Autopsy revealed third-degree burns of the legs, thighs, buttocks, hands, and face. The kidneys and liver had undergone parenchymatous degeneration. There were adrenocortical hemorrhages, edema and congestion of the lungs, congestion of the spleen, and generalized icterus. Examination of the scalp revealed recent subgaleal hemorrhage and a noncomminuted fracture of both frontal bones, extending from the left frontoparietal region to the right midfrontal region.

Examination of the Brain.—The dura had a green tinge but was otherwise normal. The piarachnoid was normal. The blood vessels over the entire surface of the brain were markedly dilated. The gyri were swollen and flattened; the sulci were partially obliterated. There was no subarachnoid hemorrhage. The circle of Willis was normal. The unci were sharply notched, but no obvious cerebellar pressure cone was seen. Coronal sections revealed marked pallor of the entire brain. No gross hemorrhages or areas of softening were seen. Cross sections of the brain stem and cerebellum revealed a similar pallor, but no gross lesions were present.

Several sections of the cerebral cortex, the basal ganglia, including the hypothalamus and brain stem, and the cerebellum were studied in celloidin with the Weigert, toluidine blue, and hematoxylin and eosin stains.

The arachnoid showed a moderate fibroblastic thickening, but no inflammatory cells or hemorrhages were present. The pial blood vessels were engorged and dilated, many showing laking of the white cells. There was marked engorgement and dilatation of the blood vessels, with prominence of the capillaries in the cerebral cortex. There was marked dilatation of the perivascular spaces, less pronounced of the pericellular spaces (Fig. 1*A*). In the white matter scattered small vacuoles were seen within the tissue, in addition to the dilated perivascular spaces.

The ganglion cells of the cerebral cortex showed a variety of changes of the Nissl substance and nucleus (Fig. 1*B*). In most cases the Nissl substance was clumped, so that no distinct granules could be differentiated. Others had lost the coarse Nissl substance, and the cytoplasm had a ground-glass appearance. The apical dendrites of some cells stood out and were tortuous. The nuclei also showed distinctive changes, chiefly eccentric placement with loss of a distinct nuclear membrane. An occasional shadow cell was seen, but a number of the cortical ganglion cells had normal nuclei and nucleoli. Similar ganglion cell changes were present in the caudate, lenticular, and thalamic nuclei. No marked glial proliferation was noted.

In the hypothalamus the ganglion cell changes were also marked (Fig. 1*C*). Many cells were rounded and swollen, with intact Nissl substance clumped around the edges of the cell. The majority of these neurons had lost their nuclei, and of those whose nuclei remained, a fair number had no nucleoli. The nuclear membrane was indistinct in most of these cells. A number of shadow cells were seen. There was little astrocytic increase.

In the cerebellum the granular cells stained less intensely than normal but were otherwise unchanged. The Purkinje cells were well preserved except for some loss of distinctness of the nuclear membrane.

In the white matter of the cerebrum the outstanding changes were found in and around the blood vessels. Several small fresh hemorrhages were present, with or without a blood vessel in the center, with hemolysis of the red cells and hemosiderin-laden phagocytes. There were also small blood vessels with proliferation of the endothelium, surrounded by a cuff of swollen astro-

cytes and compound granular corpuscles (Fig. 2*A*). Many of the blood vessels were surrounded by an area of swollen axis cylinders, as seen in the myelin sheath stains, without cellular reaction (Fig. 2*C*). There were also scattered small foci of softening, composed chiefly of gitter cells (Fig. 2*B*).

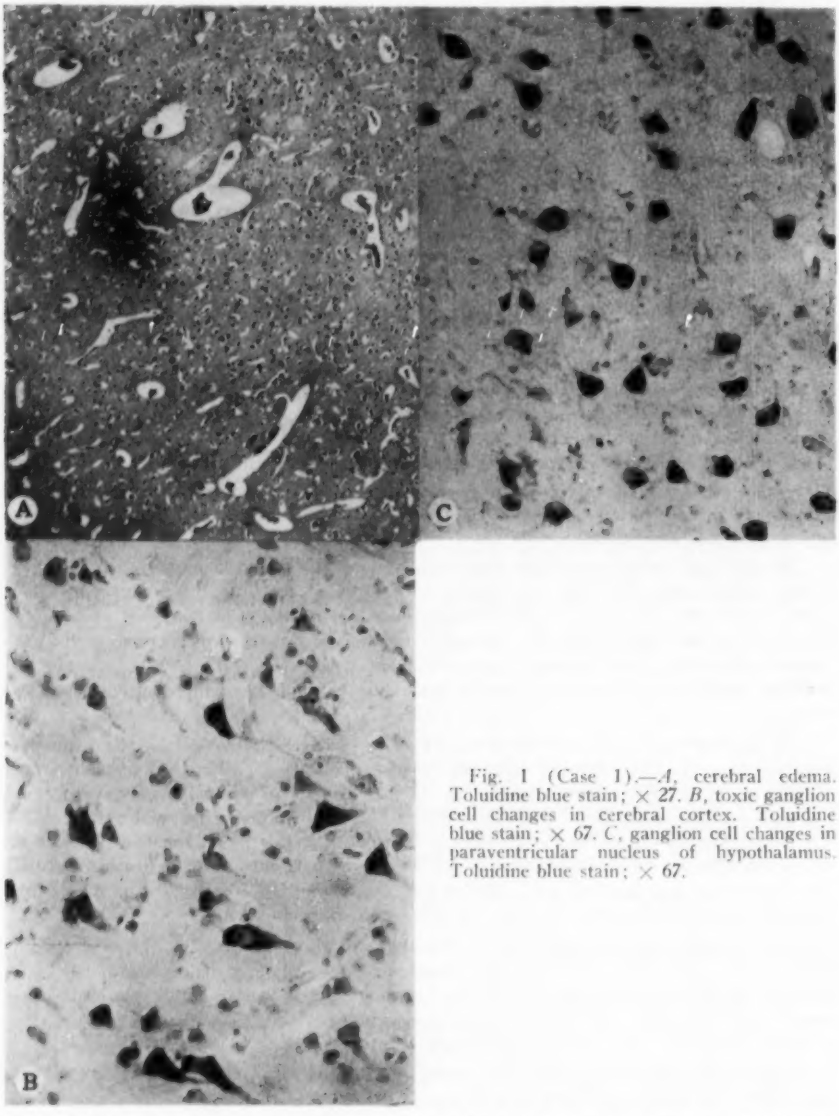

Fig. 1 (Case 1).—*A*, cerebral edema. Toluidine blue stain; × 27. *B*, toxic ganglion cell changes in cerebral cortex. Toluidine blue stain; × 67. *C*, ganglion cell changes in paraventricular nucleus of hypothalamus. Toluidine blue stain; × 67.

In Bodian stains there was loss of nerve fibers in the demyelinated areas around the blood vessels.

Case 2.—A 35-year-old factory worker suffered third-degree burns of his entire body and lived 12 days. He was treated with antibiotics, corticotropin, and a blood plasma jelly smeared over his body. He lapsed into a stupor on the 10th day and remained so until his death. The

brain showed meningitis and subarachnoid hemorrhage, as well as toxic ganglion cell changes, hemorrhages within the brain substance, and small areas of demyelination.

F. B., 51-50. A 35-year-old factory worker was warming himself at a small stove when his oil-soaked apron caught fire. Instead of rolling on the ground, he tried unsuccessfully to rip off his clothes, and the flames were finally extinguished when another worker came to his rescue.

Fig. 2 (Case 1).—*A*, demyelination around a blood vessel. Weigert stain; × 27. *B*, small areas of demyelination with replacement by gitter cells and swollen astrocytes. Weigert stain; × 33. *C*, rarefaction of myelin around a blood vessel. Weigert stain; × 67.

Examination on admission to the hospital revealed a conscious and rational subject. The entire surface of his body was burned except for the area covered by his shoes. The burns over the face, neck, abdomen, and posterior aspect of the trunk were second-degree, and there were third-degree burns involving large areas of the upper and lower extremities. His eyes were not involved. The blood pressure was 96/60, respiration rate 18, and pulse rate 100. In

addition to the extensive burns, there was swelling of the scrotum, owing to vesiculation. The heart and lungs were normal. Laboratory studies on admission revealed a hemoglobin of 10.6 gm. per 100 cc., 3,210,000 red cells, and 16,700 white cells, with 88% polymorphonuclear leucocytes. There was a trace of albumin in the urine.

Intravenous plasma was started immediately, and dressings consisting of a paste of hemoglobin and plasma were applied to all accessible body surfaces. He was started on nasal oxygen administration and was given 300,000 units of penicillin procaine G (Crysticillin) and 1 cc. of toxin-antitoxin. An initial dose of 200 mg. of corticotropin was given the afternoon of admission, and a maintenance dose of 50 mg. every six hours was continued until his death.

The day after admission the patient's clinical condition was excellent. He had no pain, took liquids freely by mouth, and required no opiates. He continued to receive plasma and fluids. The next day he was able to eat soft foods. The following day the blood urea nitrogen was 50 mg. per 100 cc., and there were 3,940,000 red cells with 12 gm. of hemoglobin per 100 cc. Two days later he was given 600 cc. of whole blood, after which he developed a chill, his temperature going up to 104.8 F. Examination of the urine showed 2 + albumin, and the hemoglobin had fallen to 10.6 gm. per 100 cc. The blood urea nitrogen was 87 mg. per 100 cc. The next day his hemoglobin had fallen to 7.3 gm. per 100 cc., and he became irrational at times but continued to take moderate amounts of liquid by mouth. Continuous transfusions were given, and the hemoglobin and red cell count rose. Despite the elevated hemoglobin, however, the patient became comatose and had to be given intravenous fluids. The blood urea nitrogen rose to 119 mg. per 100 cc., and the next day it was 225 mg. per 100 cc. The edema of the extremities, head, and trunk had subsided, but there was a marked amount of eschar formation, with destruction of the superficial tissues. The daily urinary output dropped to 425 cc., and he died on the 12th day after his accident.

Autopsy revealed confluent third-degree burns involving 95% of the body surface. There were focal embolic abscesses of the heart, lungs, left kidney, prostate, both adrenal glands, and thyroid. A confluent bronchopneumonia was found, and there was a Curling's ulcer of the stomach and fatty metamorphosis of the liver.

Examination of the Brain.—The dura and falx cerebri were normal; the superior longitudinal sinus was patent. The brain was markedly pale. The piarachnoid was somewhat cloudy, and there was some fresh subarachnoid hemorrhage, particularly over the left parietal area, just posterior to the postcentral gyrus. A small collection of subarachnoid blood was present on the medial aspect of the left frontal lobe, and a punctate hemorrhage was seen over the left occipital pole. The gyri were swollen and the sulci narrowed. The surface blood vessels were engorged. At the base, the meninges were also somewhat thickened, the unci were notched, but there was only a slight cerebellar pressure cone. The blood vessels of the circle of Willis were normal.

Coronal sections of the cerebral hemispheres showed very little ventricular dilatation. There was marked hyperemia and engorgement of the blood vessels, particularly in the centrum semiovale. In addition, in the white matter near the corpus striatum and in the corpus callosium small reddish-pink areas, which appeared to be petechial hemorrhages, were seen. In the right occipital lobe there was a small dark hemorrhage, 1 mm. in diameter, in the subcortical white matter. This appeared to be older than the other lesions. The blood vessels in the cerebellum were engorged and dilated, particularly in the dentate nuclei, and some petechial hemorrhages in the white matter of the cerebellum were observed. The brain stem showed no gross abnormalities. A portion of the cervical cord was attached and was pale, but otherwise normal.

Several sections of cerebral cortex and basal ganglia, including the hypothalamus, cerebellum, and brain stem, were studied in celloidin with Weigert, toluidine blue, and hematoxylin and eosin stains.

The arachnoid was thickened both by fibroblastic proliferation and by fibrin. In addition, there was spotty infiltration of the subarachnoid space by hematogenous cells, chiefly plasma cells. The round cells were entirely confined to the piarachnoid, and nowhere was perivascular cuffing or direct infiltration of the parenchyma noted. There were also collections of extravasated blood, with laking of the white cells. The pial blood vessels were engorged and dilated.

The blood vessels of the cerebral cortex were also markedly engorged, with dilatation of the perivascular spaces. The ganglion cells of the cortex revealed changes of both the Nissl

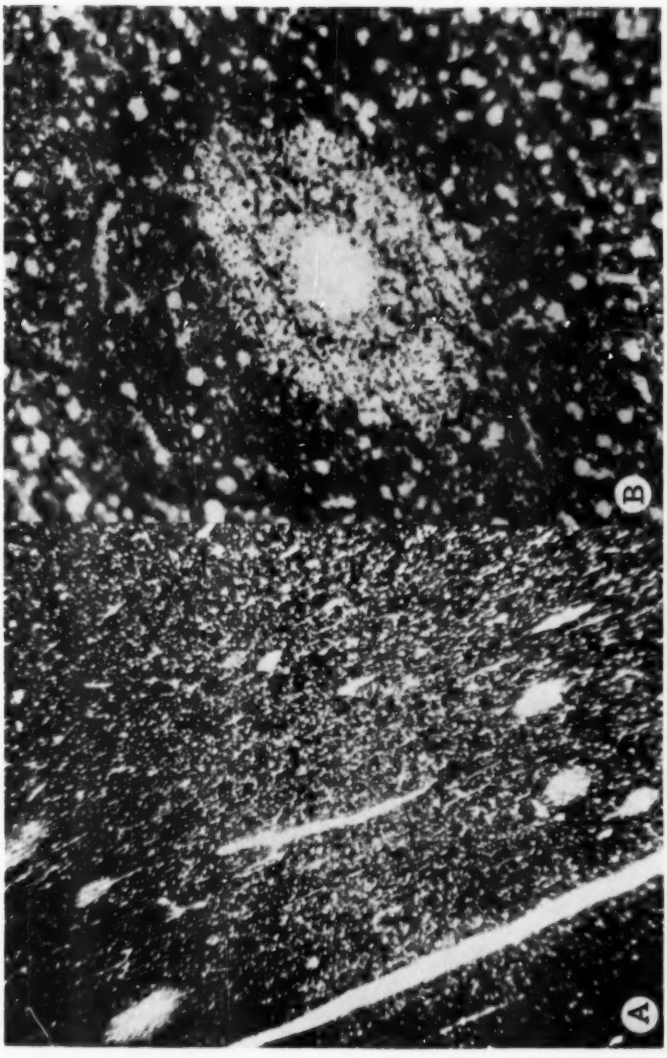

Fig. 3 (Case 2).—*A*, scattered areas of demyelination in centrum semiovale. Weigert stain; × 27. *B*, demyelination around a blood vessel. Weigert stain; × 133.

substance and the nuclei (Fig. 4*A*). Most of the cells were rounded and swollen, with loss of the Nissl granules, only a few remaining in an otherwise finely granular cytoplasm. Some cells were dark-staining and shrunken. Most of the nuclei were eccentrically placed, and many could

Fig. 4 (Case 2).—*A*, toxic ganglion cell changes in cerebral cortex. Toluidine blue stain; × 90. *B*, area of demyelination with replacement by gitter cells and astrocytes. Hematoxylin and eosin stain; × 180.

be seen extruding from the cell. A number had lost their nuclei, and those remaining had no nucleoli. Many of the nuclei were swollen, and most had lost the distinct nuclear membrane. The glial elements were increased, and these were chiefly astrocytes.

The ganglion cells in the caudate, lenticular, and thalamic nuclei showed similar changes. More of the neurons in the paraventricular, preoptic, and posterior nuclei of the hypothalamus appeared to have lost their nuclei.

The granular cells of the cerebellum were well preserved. There was a decrease in the number of Purkinje cells, and many of those remaining had lost much of the Nissl substance. They had eccentrically placed nuclei or had lost them. The neurons in the dentate nucleus were decreased in number and showed the same changes as those in the cortical ganglion cells.

The most prominent changes were seen in the white matter of the cerebrum. Under low-power magnification there were seen many scattered small areas of decreased myelin, with and without cellular reactions (Fig. 3*A*). The latter appeared to be areas of broken-up myelin and swollen axis cylinders, some around small blood vessels, others just scattered within the parenchyma. Those with cellular reactions were also of two kinds. Some had small blood vessels in the center, and these were cuffed by swollen astrocytes and compound granular corpuscles (Fig. 3*B*). Others had no central blood vessel but were small areas in which the myelin and nerve fibers were replaced by gitter cells and swollen astrocytes (Fig. 4*B*). There were scattered small fresh hemorrhages, with red cells still well preserved. In some instances, these consisted of a central blood vessel cuffed by a ring of fresh red cells. Some of these blood vessels had a small ring of glial cells and then an outer, larger zone of red cells. In Bodian stains, many of the nerve fibers were swollen. In the areas of demyelination the nerve fibers were destroyed.

Sections of the cervical spinal cord revealed fibroblastic thickening of the piarachnoid but no hematogenous infiltration. There was engorgement and dilatation of the pial blood vessels, as well as of the vessels of the parenchyma of the spinal cord. The nerve roots had lost most of their myelin, and both the myelin sheaths and the axis cylinders were swollen. The anterior horn cells were decreased in number, and those that remained had normal Nissl substance, but the nuclei were eccentrically placed or missing. No small areas of demyelination, as described in the cortex, were found, but some swelling of the myelin sheaths around blood vessels could be seen.

Elastica stains revealed the elastic membranes of the blood vessels to be normal.

COMMENT

Neuropathological Features.—Only two detailed neuropathological reports of brain changes in severe burns were found in the literature.

Globus and Bender [2] reported the case of an 8-year-old boy who had extensive second-degree burns. At first he was anuric and had episodes of vomiting. He became refractory, soiled and wet himself, and it was believed that his symptoms were due to emotional problems rather than to brain damage. He declined mentally, became delusional and abusive to the nurses, and died six months after the burns. Examination of the brain revealed dilated ventricles. The ganglion cells were swollen and rounded and showed chromatolysis and displacement and pyknosis of the nuclei. There were diffuse, degenerative changes in the white matter, with an occasional large, circumscribed area of demyelination. The small areas appeared as vacuolations, seen in both the cerebrum and the cerebellum. The larger areas of demyelination were usually around a blood vessel. These areas were crowded with gitter cells. There was advanced gliosis throughout the brain, especially the subcortex. The authors stated that early cases showed only hyperemia. They cite Brancati,[11] who subjected guinea pigs to experimental burns and found hyperemia and small hemorrhages in the early stages and an increase in glia in the more advanced cases. He found that pathological changes of a similar nature were produced by horse serum. Globus and Bender felt that the lesions they found were similar to those seen in early multiple sclerosis.

Walker and Shenkin [10] reported six cases of extensive body burns in which the brains were studied. The patients showed varying degrees of disorientation and drowsiness, leading to stupor. Muscular twitches were noted. The authors observed that often signs of renal and hepatic damage had begun to lessen and the patients had begun to improve clinically, only to have sudden respiratory failure. Five of the six patients died about the fourth day. The sixth patient lived 62 days and died of a pulmonary embolus. This last patient showed evidence of a less pronounced degree of toxic cell changes in the brain than did the other patients, and there was little, or no, evidence of increased intracranial pressure or medullary compression. The other patients showed severe cerebral edema. The ganglion cells showed toxic degeneration, especially in the cortex and hypothalamus. This consisted of swelling of the cells and disappearance of the Nissl substance. The nuclei were usually eccentric and occasionally absent. They were often swollen and were in all stages of disintegration. In some cases the nucleus had become pyknotic. The cytoplasm was pale and occasionally contained vacuoles. Many shadow cells were noted. The basal ganglia and brain stem nuclei were less involved.

Walker and Shenkin believe that the deaths were due to damage of the central nervous system, with failure of the medullary centers as a result of compression edema and cellular lesions. They cite Riehl, who reported cerebral edema in nine cases.

Spielmeyer [12] stated that acute swelling of ganglion cells occurs in burns. Freeman [13] stated that burns probably act through disturbance of the water metabolism and bring about minor degenerations, with variable edema and small hemorrhages. The capillary endothelium in the brain is usually considerably swollen and may have undergone fatty degeneration. Weil [14] noted that foci of small ring-like necrotic areas, which are frequently surrounded by hemorrhages, have been described as occurring after severe burns. He referred to the lesions as brain purpura. Scheinker [15] observed that vasoparalysis may develop as a result of severe burn injuries. Pack and Davis [16] described hyperemia of the brain and meninges, with the white substance showing puncta vasculosa. The arachnoid vessels, they stated, may be engorged and contain occasional thrombi.

The neuropathological findings in our cases seem to fall into three main groups: (1) the cerebral edema and blood vessel changes, (2) the ganglion cell changes, and (3) the alterations in the axis cylinders and myelin.

The cerebral edema was more marked in some portions of the cortex than in others and was seen grossly as swollen gyri and obliterated sulci. Microscopically, the perivascular spaces were dilated, with relatively little dilatation of the pericellular spaces. The edema was more evident in the first case than in the second.

The hyperemia was observed grossly both on the surface of the brains and in coronal sections. There was some subarachnoid hemorrhage in the second case. Within the parenchyma the blood vessels were markedly engorged, and the capillaries in the gray matter were especially prominent. In the white matter frank hemorrhages were present, but many were small ring-like hemorrhages around a smaller cuff of glial cells, which, in turn, surrounded blood vessels whose endothelium was either swollen or broken down. This corresponded to the brain purpura described by Weil.

The ganglion cell changes were of the toxic type. Most of the cells were swollen, with loss of much of the Nissl substance, and had either eccentric or extruded nuclei. These changes were fairly consistent in most areas studied, but there appeared to be somewhat more loss of nuclei and more shadow cells in the hypothalamus. The glial proliferation, chiefly astrocytes, with neuronophagia, was more prominent in the second case. The Purkinje cells of the cerebellum were not markedly affected in Case 1, but were definitely decreased in number and showed some chromatolysis and eccentric nuclei in Case 2.

Two chief changes were found in the myelin. In many small areas the myelin was swollen, giving a rarefied appearance, seen chiefly around blood vessels, without cellular reaction. These areas were commoner in Case 2. The second type of myelin change consisted of small areas of destruction of the myelin and axis cylinders, with replacement by gitter cells and some swollen astrocytes. Some of these were also around blood vessels, but others gave the appearance of small foci of softening within the parenchyma. In the myelin sheath stains, both changes stood out as small areas of demyelination. In the nerve roots of the spinal cord of Case 2, there was demyelination and swelling, both of the myelin sheaths and of the axis cylinders.

Clinical Features.—The two patients in this report survived only 12 and 16 days, an insufficient time in which to observe many neurological or behavioral changes. Many of the ganglion cell changes were irreversible and could lead to a postencephalitic-like picture, as well as seizures. The changes in the white matter might produce neurological signs, although the areas of destruction were smaller than the usual plaques seen in multiple sclerosis and therefore probably would not show the marked changes usually seen in that disease. However, glial scars could be formed and might cause continued seizures.

There have been a number of reports of clinical changes referable to the central nervous system observed in patients with severe burns. Roth [3] reported the case of an 8-year-old girl with second- and third-degree burns of 30% of the surface of her body. Twenty days after the burns she became comatose and had a series of generalized convulsions. She developed aphasia, had continuous athetotic movements of the right hand, and deteriorated mentally. The spinal fluid was normal. A pneumoencephalogram taken four months later revealed marked hydrocephalus and cortical atrophy.

Kruse [4] reported the case of a 14-month-old infant who suffered extensive second-degree burns but showed no neurological signs until one month after the accident, when it had tonic convulsions. The child later developed blindness, progressive hydrocephalus, and mental deterioration. There was subsequent recovery from the blindness. Cobb and Lindemann,[5] in a study of persons burned in the Cocoanut Grove fire, described one woman with neurological signs which they felt were due probably to carbon monoxide poisoning rather than to a direct effect of the burns. Schachter [6] reported three cases of children who developed seizures after burns and one case of a child who became a severe behavior problem. He felt that these children were affected because they already had some underlying pathological disturbance of the brain, such as a vascular, or parenchymatous lesion, and the cerebral edema and hemodynamic difficulties brought on by the burns precipitated the symptoms. Crocco [7] reported a case of severe encephalitis of brief duration,

following burns, accompanied by amaurosis, deafness, and choreoathetotic movements. Morrison,[8] in a study of burns in children, reported that some showed drowsiness and signs of increased intracranial pressure, as well as muscular rigidity and muscle twitching. Two children had convulsions. Both had elevated spinal fluid pressures (250 and 360 mm.). She stated that the neurological signs usually lasted only 2 to 3 days and in no case exceeded 10 days. Necropsy in two cases revealed only cerebral edema.

A provocative report is that of Hughes,[9] who recorded a case presentation of a 21-month-old child with 50% of the body surface burned. The baby was spastic, had involuntary movements, and made swallowing, yawning, and champing movements of the jaws. There was a suggestive sensory level at C_7 with an apparent transverse spinal cord lesion. The cerebrospinal fluid was normal. Hughes made a provisional diagnosis of demyelination following burns but, unfortunately, gave no follow-up report.

The chief clinical features observed in these reports included convulsive seizures, postencephalitic-like symptoms, and mental deterioration. Although there were very few pathological reports, these findings can be explained by the changes we have observed or can anticipate. The convulsions are due probably to these three pathological conditions: (1) the cerebral edema, (2) the toxic ganglion cell disease early in the process, and (3) the formation of glial scars after the acute reaction has subsided. The postencephalitic-like picture, as well as the mental deterioration, can also be ascribed to the ganglion cell disease. The case report of Hughes[9] is of particular interest in that he postulates a demyelination of the spinal cord due to burns. The degree of demyelination was much greater in the patient with 95% of his body surface burned (Case 2) than in the boy with only 40% involved. Although we have only these two cases to judge by, this observation may indicate that the more extensively burned cases will have greater damage to the myelin, in addition to the ganglion cell disease, whereas those with less severe burns will show chiefly the neuronal changes.

It is not within the scope of this paper to attempt to account for the changes found. There is, apparently, still much debate as to whether toxins are liberated in patients with severe burns, or whether the alterations are due to a circulatory, and therefore an anoxic, state. Cullumbine and co-workers have reported the existence of a polypeptide leucotaxine that they have isolated experimentally from the burn exudate, which on subcutaneous injection into rabbits caused marked local edema and a reproduction of the blood changes as seen in severe burns. Although this may not be the final answer the changes which we have found are in keeping with a toxic condition.

CONCLUSIONS

The neuropathological findings of two patients with extensive burns, who survived 12 and 16 days, respectively, are reported.

There was cerebral edema and blood vessel changes, including hyperemia, small hemorrhages, and brain purpura.

The ganglion cell changes were chiefly toxic in character, consisting of swelling, chromatolysis, and eccentric or extruded nuclei, somewhat more marked in the hypothalamus.

There were small areas of demyelination, due either to swelling of the myelin sheaths or to destruction of the normal tissue with replacement by gitter cells. These changes were more marked in the more extensively burned case, and the suggestion is made that the myelin damage is severer in the extensively burned patient, whereas only the neuronal changes are seen in those less severely burned.

These changes suggest a toxic, rather than an anoxic, effect on the central nervous system.

Several of these pathological alterations were irreversible and may cause convulsions, mental deterioration, or a postencephalitic-like picture.

REFERENCES

1. Blocker, T. G., Jr.: Newer Concepts in the Treatment of Severe Extensive Burns, Surgery **29**:154, 1951.

2. Globus, J. H., and Bender, M. B.: Disseminated Toxic Degenerative Encephalopathy Secondary to Extensive and Severe Burns, J. Nerv. & Ment. Dis. **83**:518, 1936.

3. Roth, N.: Encephalopathy Due to Burns, Arch. Neurol. & Psychiat. **45**:980, 1941.

4. Kruse, F.: Enzephalitis und Amaurose nach Verbrennung, Deutsche med. Wchnschr. **54**:1039, 1928.

5. Cobb, S., and Lindemann, E.: Symposium on Management of Cocoanut Grove Burns at Massachusetts General Hospital: Neuropsychiatric Observations, Ann. Surg. **117**:814, 1943.

6. Schachter, M.: Encephalopathies and Character Disorders Following Burns in Infants, Acta psychiat. et neurol. **25**:285, 1950.

7. Crocco, G.: Case of Encephalitis Following Burns, Pediatria **57**:551, 1949.

8. Morrison, B.: Study of Burns and Scalds in Children, Arch. Dis. Childhood **22**:129, 1947.

9. Hughes, L.: Burns with Cerebral Complications, M. J. Australia **2**:122, 1947.

10. Walker, J., Jr., and Shenkin, H.: Studies on the Toxemia Syndrome After Burns: Central Nervous System Changes as a Cause of Death, Ann. Surg. **121**:301, 1945.

11. Brancati, R.: Sulla patogenesi della morte per ustione, con speciale riguardo allo studio del sistema nervoso, Policlinico (sez. chir.) **31**:233, 1924.

12. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Springer-Verlag, 1922.

13. Freeman, W.: Neuropathology, Philadelphia, W. B. Saunders Company, 1933.

14. Weil, A.: Textbook of Neuropathology, New York, Grune & Stratton, Inc., 1945.

15. Scheinker, I. M.: Medical Neuropathology, Springfield, Ill., Charles C Thomas, Publisher, 1951.

16. Pack, G. T., and Davis, A. H.: Burns: Types, Pathology and Management, Philadelphia, J. B. Lippincott Company, 1930.

RELATIONSHIP BETWEEN RORSCHACH DETERMINANTS AND PSYCHOSIS IN BARBITURATE WITHDRAWAL SYNDROME

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THIS PAPER is a replication of part of a prior study [1] which suggested certain significant correlations between specific Rorschach determinants and psychosis in barbiturate addicts following abrupt withdrawal of the drug. In order to manifest the withdrawal syndrome, the subject must receive sufficient barbiturates to cause continual intoxication for several months. When the barbiturates are abruptly withdrawn, there is a characteristic abstinence syndrome. This syndrome consists of convulsions or psychosis or both.[2] The psychosis is temporary, manifested by hallucinations, delusions, anxiety, agitation, insomnia, confusion, and disorientation. Although the withdrawal symptoms are often severe, there is no evidence at the present time of any residual effect directly attributable to the addiction or the withdrawal.

In this earlier study five former morphine addicts volunteered as subjects. They were prisoner patients at the United States Public Health Service Hospital, Lexington, Ky. The addiction period lasted 92 to 144 days. During withdrawal three of the subjects became grossly psychotic, and two had no psychosis or psychosis was mild. Rorschach and other projective techniques were administered to this group before the start of the chronic intoxication period, once during intoxication, once during withdrawal, and once several months subsequent to the withdrawal period. A retrospective examination of the Rorschach protocols obtained prior to chronic intoxication * revealed a dichotomy in three Rorschach determinants which clearly separated those who became grossly psychotic from those who did not. The subjects who became grossly psychotic had a paucity of both color (C) and human fantasy (M) responses and a high F + %, while the subjects who did not become psychotic or whose psychosis was mild had a comparatively large amount of C and/or M responses and a low F + %.

PRESENT STUDY

The reactions of 14 male patients were studied. These patients were admitted to the United States Public Health Service Hospital, Lexington, Ky., ostensibly for the treatment of opiate addiction, but they were also addicted to barbiturates. All of these subjects experienced the barbiturate withdrawal syndrome when medication was terminated abruptly. For nine of the subjects the severity of the withdrawal was not known until after the Rorschach tests were scored. As in the previous study, the Beck method [2] was used in scoring the Rorschach tests.

National Institute of Mental Health.

* The Rorschach responses obtained prior to intoxication and those obtained several months subsequent to the withdrawal period were both qualitatively and quantitatively similar with respect to each subject.

On the basis of the previous research, it was predicted that those subjects who became grossly psychotic during withdrawal would have few C and M percepts and a high F + %, as compared with those subjects who exhibited no psychosis or in whom psychosis was mild.

The severity of the psychosis was clinically determined by the medical personnel of the Research Center for Drug Addiction, United States Public Health Service Hospital. Of the 14 subjects, 8 were considered to fall in the gross psychosis group and 6 in the mild or no psychosis group. Only subjects with 10 or more responses on the Rorschach tests were included.

The statistical technique used to analyze the data was the U-technique,† a non-parametric, rank-order statistic, for determining the probability with which observed scores in one group were larger than the observed scores in another, by chance alone.

Individual Sum C + M and F + % for All Subjects.

Psychosis			No Psychosis (or Mild Psychosis)		
Subject	Sum C + M	F + %	Subject	Sum C + M	F + %
1	1.5	83	9	7.5	64
2	1.5	75	10	4.0	82
3	1.0	83	11	3.5	68
4	1.0	75	12	3.5	52
5	1.0	100	13	3.0	88
6	1.0	85	14	0.5	89
7	0.5	67			
8	0.0	78			
Means	0.9	80.8		3.7	73.8

RESULTS

The individual sum C + M ‡ and F + % are presented for each subject in the accompanying Table. By inspection it can be seen that the F + % of the subjects who became grossly psychotic does not appear to be significantly different from those who did not become psychotic or in whom psychosis was mild. The sum C + M scores of the subjects who did not become psychotic, or in whom psychosis was mild, was significantly larger than the sum C + M scores of the subjects who did become psychotic ($P < 0.03$).

COMMENT

The results for the sum C + M conform to the predictions. Although the outcome for the F + % is in the predicted direction, it does not approach an acceptable level of confidence. The failure of F + % to reach an acceptable level of confidence suggests the possibility that F + % is not a discrete personality determinant but fluctuates in relationship to other Rorschach scoring categories. On the

† References 4 and 5.

‡ Although the number of responses (R) discriminates between those subjects who became psychotic and those who did not (subjects who became psychotic had less R, $P < 0.02$), this scoring category was not included because of the following factors: (*a*) In the original five subjects (the basis for prediction in the present study of 14 subjects) R did not discriminate between the two groups; (*b*) if the N of 14 is increased to 19 by including the original five subjects, the predictive value of R decreases ($P > 0.15$), while it increases for Sum C + M ($P < 0.01$) and F + % ($P < 0.10$).

other hand, probably M and C are psychologically more independent determinants and can fluctuate independently of the other scoring categories.

The Rorschach results of subjects who became grossly psychotic may indicate a failure to utilize affective expression and fantasy living in life situations. The fact that they develop "full-blown" psychosis in the barbiturate withdrawal syndrome (an extreme physiological stress) suggests the hypothesis that subjects who do not utilize either affective expression or active fantasy do not have appropriate resources to cope with this type of extreme stress. Human fantasy responses of poor quality or regressive use of color (C or CF greater than FC) seemed as effective as human fantasy of good quality or mature color responses in allowing the subject to avoid psychosis under the stress of withdrawal.

The predicted relationship found between the sum C + M and the severe psychosis during the barbiturate withdrawal and the reported failure of some investigators [6] to obtain significant results in other Rorschach predictive studies may be due to the homogeneity of this population (all subjects were opiate addicts) and to the sameness of the stress situation. It is very likely that as the heterogeneity of a population and the variety of stress situations decrease, the probability of successful prediction of behavior under stress increases.

SUMMARY

A Rorschach test was administered to 14 former opiate addicts several months after they had recovered from the syndrome that follows abrupt withdrawal of barbiturates.

Eight of the subjects became grossly psychotic within a few days after the abrupt withdrawal of the barbiturates, and six were not psychotic or had only a mild psychosis. When psychosis appears, it is only of a temporary nature.

On the basis of a previous study it was predicted that the subjects who became grossly psychotic during withdrawal would have few C and M percepts and a high F + %, as compared with the subjects who exhibited mild psychosis or no psychosis.

In the present study those subjects who became grossly psychotic during withdrawal had less sum C + M percepts at a statistically significant level and a higher F + %, but not at a statistically significant level, than those subjects who experienced no psychosis or in whom psychosis was mild.

These data support the hypothesis that persons who do not utilize either affective expressions or active fantasy in life situations do not have resources to cope with the tensions associated with extreme stress of this type.

REFERENCES

1. Kornetsky, C. H.: Psychological Effects of Chronic Barbiturate Intoxication, A. M. A. Arch. Neurol. & Psychiat. **65**:557-567, 1951.

2. Isbell, H.; Altschul, S.; Kornetsky, C. H.; Eisenman, A. J.; Flanary, H. G., and Fraser, H. F.: Chronic Barbiturate Intoxication, Arch. Neurol. & Psychiat. **64**:1-28, 1950.

3. Beck, S. J.: Rorschach's Test, New York, Grune & Stratton, Inc., 1949, Vol. 1.

4. Mann, H. B., and Whitney, D. R.: On a Test of Whether One of Two Random Variables Is Stochastically Larger Than the Other, Ann. Math. Statist. **18**:50-60, 1947.

5. Moses, L. E.: Non-Parametric Statistics for Psychological Research, Psychol. Bull. **49**:122-143, 1952.

6. Windle, C.: Psychological Tests in Psychopathological Prognosis, Psychol. Bull. **49**:451-482, 1952.

ALTERATIONS IN THE "FIELD" IN A BRIEF DEPRESSIVE EPISODE

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PSYCHOANALYSIS has been from its beginning a study of relationships among persons (and classes of persons). These relationships are "fields," analogous to fields as conceived in modern physics. Operationally, psychoanalytic practice has been oriented toward the field—in the study of transference and countertransference attitudes. Theoretically, however, the logical model classically used has been that which deals with self-acting entities and forces, based upon Newtonian mechanics.[1] In this paper we have attempted to describe a brief depressive episode in terms of the changing fields of which the patient felt herself to be a part at various periods in her illness and recovery. We believe that such an alteration in language of description and in the logical model upon which the language is based makes for a greatly more flexible theoretical construction, while at the same time it loses nothing essential.

In two other respects as well this report represents something of a departure from the traditional type of paper in this area. The first of these is the briefness of the contact with the patient, the whole comprising only four interviews and a telephone conversation. Notwithstanding the limitations of such a small series of interviews, the patient in a remarkably comprehensive way described what appear to us to be the significant events in this depressive episode. This achievement of description parallels the patient's ability to recover spontaneously from a more serious depressive episode interpolated in the course of a chronic anxiety state.

The second departure is the verbatim reproduction of the patient's statements which form the basis for the conclusions reached. It appears to us that it is of crucial importance in this complex field for the observer to report data in a manner direct enough to allow full comparison of data and conclusions, to the end of rendering a fuller consensus possible.

CLINICAL MATERIAL

We wish to explore the problem of pathogenesis in this area by using material derived from three interviews with a woman who described the onset and resolution of a depressive episode with quite unusual clarity. The material to be cited was recorded on tape and transcribed therefrom. We have rearranged the patient's words to form discipline paragraphs, to which we have appended a running comment; and after the citing of the material we have reviewed the problem with the theoretical formulation which appears appropriate.

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This study was done at the Boston Psychopathic Hospital and was supported by funds from a United States Public Health Service grant Project M-354C.

First, the patient describes her relationship to her husband. He is moody, demanding, and, lately, suspicious.

1. "Maybe my husband has affection, he supports us and he's home every night and like that, but even my son notices there's no outward show of affection; he'll never give you a kiss or show any signs of affection. . . . His sister-in-law has a daughter who is very, very mean; she's really a nasty girl, takes full advantage of her mother and appreciates nothing. . . . She told me one time, she used to go with him before I did, and she told me, she said, 'You know, it's a funny thing, but my daughter reminds me so much of your husband when he was young.' Now her daughter will come in from work, and her mother has taken care of the two children all day and she'd like to have a little conversation at night; but she'll come in, she'll eat, and she won't say a blessed word; she'll sit down and read or watch TV, and she never says a word to her mother. And her mother says she is just the same as my husband was."

But at the same time she describes herself as unusually dependent upon her husband.

2. (*a*) "Why is it other people don't let things like that bother them? Their husbands can say what they like, and they never pay any attention. I wish I was like that." [Doctor: "It's too important to you what your husband says?"] "Yes, it is, I don't know why. It shouldn't be, he's only a man; he shouldn't frighten me and give me the feelings that I get. He's the only one that makes me feel like that. He started with his dirty looks—his dirty looks just kill me—I could just melt. . . . I get a squeezing feeling in here, just as if you were wringing out clothes, when he gets that grouchy look, but then I pretend I'm not paying any attention."

(*b*) "My husband has kind of a fast temper. He'd never hit me or anything like that, but the thing that put it in my mind that he might is, for instance, just recently his young brother is having a little friction with his wife, and my husband said, 'Why if I were married to her, I'd beat her up three or four times a week.' So it sort of put it into my mind that he was capable of hitting me if he ever got mad enough, which I don't know exactly what I would do if he would ever hit me. He never has, but it's that feeling that something really big might happen that gets me excited."

The patient has been married for 13 years; for the past 6½ years she has lived in the country. A city girl, she has never been a great talker or very much interested in particular people, but it has always been a source of great satisfaction to her to be in the midst of many people. She goes to town for the purpose of mingling with the crowds and relieving a rather chronic feeling of loneliness.

3. (*a*) "It's very, very quiet where I live. There are houses around just as close as in the city, but there's nobody in them. All the men and women, they work. . . . All day long you're quiet. Now, sometimes my boy goes to school, and unless one of the tradesmen comes to the house, the laundryman or someone, until the boy comes home at three, I never open my mouth. So the feeling is being all alone."

(*b*) "We weren't what you'd call a clannish family. . . . Even when I was in school I didn't do much talking. . . . Before if I met people, I didn't care if I'd see them again or not, but now, the girl I met in the hospital when I had the baby, I talk to her on the phone and I like to keep in contact with them. Maybe it's from being alone so much for six years that's changed me. When I was among people it didn't bother me to be alone, but now that I've been alone I think that that's what's making me reach out to people more."

(*c*) "Before the baby was born, I used to go into Boston and go to one of the morning movies, and I would just walk through the stores and then I would go home . . . and I didn't mind staying there the rest of the week. I always liked to go into Boston and walk up and down Washington Street, go in and out of the stores and see all of the people. I just like to be where there are a lot of people."

She is sensitive to loneliness but at the same time finds that she is very susceptible to the troubles that other people have; if she hears of someone getting hurt, it hurts her.

4. (*a*) "If I see something happening to somebody or if somebody tells me about something, I get awfully nervous. That's why I think half the time that I should stay home and mind my own business and not listen to people. . . . My sister says, 'You let other people bother you and you shouldn't.' If someone tells me that they've had a great trouble and then they describe it, I can feel so bad for them."

(*b*) "If I should be in Boston and see somebody very old and I don't even know who they are. If I just see them walking down the street, I feel like crying. . . . And when I look at my mother. My sister said that I shouldn't lean on my mother. My mother is 74 and she'll die. . . . My good brother died, too. I'm not close to my husband. There's no closeness at all; so I feel alone."

(*c*) "Maybe my husband has affection . . . but even my son notices that there is no outward show of affection. It has switched on to me, for there was one time I gave the boy a big kiss and he says, 'You didn't kiss me for a long time.' That cold feeling, it seems to rub off on you."

When separated from her husband by distance or by an alienation in the relationship, she tends to feel upset in a specific way: She stiffens up, gets hardened. She feels cold, paralyzed, unable to move freely.

5. (*a*) "He gets into one of those balky moods. . . . Somebody at work said something that he didn't like and he'll take it out on me at home, and I'm wondering if it's something that I did, and then maybe three or four nights later he'll explain what upset him. . . . I just give him his meals and he goes off to work the next day, and it's the same thing the next night and, as I say, three or four days later things will thaw out. . . . I feel very tense and tight; I pretend it isn't bothering me, but it is. . . . I just tighten right up. . . . My arms and legs, they just seem to stiffen up."

(*b*) "The last couple of years I feel hard. He talks and I have a heart of stone. I haven't, but I have learned the harder you are the better off you are. . . . If you're the least bit tenderhearted, you'll get walked on. . . . If you put up a good hard front, you won't get stepped on."

(*c*) "So I guess I got the reputation of being pretty hard, but naturally I'm not. My sister said that my brother who died once said that if I didn't stop being so soft I'd crack up, and if he were alive today, John would say, 'I knew it was coming.'"

A frightening fantasy may be seen with some clarity in the material below, where an anonymous doctor is carrying out a procedure so horrible that it frightens a student nurse.

6. "I was over at the Lying-In (Hospital) . . . in the clinic. . . . There was a girl talking to me in the waiting room . . . telling me about her case, and it happens we were in connecting examining rooms . . . and the doctor started to do something, and she started to moan and groan, and I started to get awful cold. . . . I felt like getting right up and going. . . . When I got out of there I was on the street car, my neck got stiff as a board, and I couldn't turn my head. . . . About two hours later it vanished. . . . I'll tell you also what made me feel terrible; two student nurses were at the connecting door, and one of the nurses was even biting her fingers. . . . I don't know what they were doing to her, but it must have been something terrible, and from looking at the nurses and hearing the moanings and groanings it was awful."

On the other hand, at times she is able to get very angry with the husband and sometimes can express it in one way or another. Most of the times that she describes being able to express herself in this way involve a defense, not of the patient herself but of her child. She feels violent, active, hot, destructive.

7. (*a*) "There was a girl 14 years old, and when my boy was about three years younger than he is now, he got into some words with her, and she gave him a crack across the face, and he came home crying. One of the neighbors told me she had smashed him. So I started to get awfully hot and awfully mad, and I went out on the street and told her where to get off, and I came back and my husband was in the yard and I told him about it, and he said, 'Don't bother me with things like that,' he said, 'When the kids fight let them fight.' I said, 'Don't you realize how much bigger and older she is than he is?' And you know I don't usually say anything out loud so the neighbors can hear it, but I got so mad at him I guess everyone could hear it that night. I told him to stay out in the yard and dig his fool head off, and I went into the house. A little while later the girl came back with two of her older sisters, and we had a regular brawl that night. I was inside and they were outside, and I was fighting them and my husband was sitting at the table. Finally he didn't like the sound of their words, so he got up and told them off, but after it was all over, I went out of the house, I was so mad at him, I was fighting for the boy, and then at the very tail end he decided to do something about it. I went out of the house and I started to run, and there's a long narrow country lane out where we live, and I ran the whole length of it."

(*b*) "I was hot; when I get mad I get hot. If I get into an argument or get into a fight at home, I don't know whether some people screech and let steam off or whether they use profanity and that eases them, but I'll start cleaning out bureau drawers or I'll get old Christmas cards and old bills and tear them up, and I don't know whether it's the sound of the tearing or what that eases the tension or what, but I do that all the time."

However, at the same time she says that she does not have "deep maternal feelings" for little babies. This theme becomes progressively more important as she talks about the development of her illness. We find that very small babies are frightening; they are not people; they are unresponsive.

8. (*a*) "I'm awfully afraid of very small babies. I felt the same way when I got my other boy. . . . Very small babies under three months, they make me feel awful peculiar. I don't know if it's just because I think something might happen to them. . . . Small babies are terrible. . . . They don't look like people. . . . They just lay there and they have that film over their eyes that hasn't cleared up. . . . They don't know voices and they don't know you. . . . I get a lonesome feeling. . . . All alone in the world. . . . It seems awfully quiet."

(*b*) "For three months it was miserable . . . this woman across the street . . . she says she doesn't understand it, this feeling about small babies. She kept telling me that's the time they're the best and they'll never be as sweet as that again, and enjoy them while they're little. She could not get it into her head why I think they're nice after they pass three months. . . . It's just for the first three months. Perhaps I am not motherly the way I should be. I took care of him all right, I made sure his formula was made, I bathed him every day and took care of his clothes. I didn't neglect him, but it's just that I don't have that feeling."

The relationship to very small babies is ambivalent; in one way she is very much afraid of anything happening to the child, e. g., smothering. Here we note resemblance to her own fears, in that when things are very bad the patient herself feels as though smothering, as though the walls are coming in on her.

9. (*a*) "The house doesn't feel like that now—I don't feel like I'm getting smothered. I don't feel so edgy now that the baby seems more friendly. Well, he is more friendly. . . . I worried over him. . . . You have to be careful of small babies in case the blanket gets over their heads or in case they might choke. . . . It's in the paper all the time, babies smothering in carriages and cribs."

(*b*) "[I felt] closed in the house. When I was taking care of the baby, it seemed as if the ceiling was coming down and the wall was coming in. . . . I thought I was going crazy. My sister's house didn't crowd in on me the way mine did."

The baby is frightening, inhuman, unfriendly; we note particularly that the absence of a response is to the patient a hostile response. To us it appears, thus,

that the patient needs to be protected against hostile feelings by a friendly response from another person; in the absence of such a response she is subject to flooding by aggressive feelings which threaten her whole concept of herself and which must be (1) expressed—but she can express these feelings only when she is protecting someone else—(2) immobilized—as we note in the stiffening experience—or (3) directed inward—and this state is the one in which the patient describes the onset of depression. Specifically, we see that there are several components, the lack of contact with the husband, the factor of loss of sleep, the inability to impose on her mother, and the unfriendly, alien character of the impression which the baby makes upon her.

10. (*a*) "I'm better, I know I am; I'm keeping the house going and things don't look as black, but it keeps coming to my mind, 'What if it ever happens again, that awful, awful feeling?' I never had it before . . . never that low . . . like I wanted to give up. I didn't want to keep on going."

(*b*) "It seems to me I was going along all right for about a month . . . when I started to get that tired all-gone feeling . . . when everything started to fall apart . . . I was getting crankier and crankier all the time, and I thought it was because I wasn't getting much sleep. At first the baby was eating every three hours, and my husband thought my mother was taking care of him . . . but you see my mother would help me with the baby, but I got up out of bed and heated the bottles. . . . It was every night like that with no straight sleep. I was getting tireder and tireder all the time and my body just got tired, and that was when I stopped eating. I just didn't seem to have enough strength to keep the house going."

(*c*) "I felt the least my husband could do was his share . . . but he says, 'I thought with two women in the house, why should I get up?' . . . He has no patience with sickness of any kind, and even if he's sick he keeps right on going. . . . He's never had patience with sickness from the first, and it seems to me it's got worse. But we never talked about that much. When he's sick we've had good long conversations, but when it's someone else he's very, very sharp and abrupt, and you get it over as fast as you can."

(*d*) "I couldn't get out and my mother said, 'While I'm staying here for a short while why don't you go out and take advantage of it?' A couple of times I did, and my neighbor, when she'd go shopping, she'd take me with her, but I didn't like to do that, see, I don't like to impose on people, and it seemed sort of like imposing on my mother to go out and leave the baby with her. . . . If there was any way out of a situation, I would never ask anybody to do anything for me, ever. Unless it was the last resort and I had to. . . . I don't like to bother people. . . . It's nervy, if it's not an actual necessity."

We find she has somewhat the same attitude toward sickness as that of her husband. It is of particular note that she attempts to deny the illness by refusing to adopt the (recumbent) position of the sick person; this posture is, so to speak, the "outside," or the appearance to the external observer of the condition of sickness.

11. (*a*) "If I get sick I get afraid. I'm afraid to get sick. As long as I can I keep on my feet, and as sick as I get I keep on going; yet I'm always afraid if I go to bed I won't get up. Unless I'm very sick I never go to bed, and in the back of my mind I'm afraid to get sick."

(*b*) "If I get sick what would happen? He isn't the kind that could keep things going. If it was some men, they could take over for a couple of days and get some meals on the table and keep a few pieces of clothes ahead. In a case of sickness he sort of gets panicky too, and in an emergency he never knows what to do."

At the breaking point the sense of effort in suppressing distressing proprioceptive sensations disappears with a collapse in self-esteem and a severe sense of failure. In the resultant detached state the patient appears to herself remote and

worthless; this attitude is one which she fears and believes is shared by the "other people," those who are looking at her with the same lack of sympathy with which she views herself.

We may note a number of consequences of this type of suppression of proprioceptive information; the patient describes a feeling of emptiness inside, an "all-gone" feeling. Many other patients with depressions have very acute feelings of having no insides, no guts. The desires of human beings, which are very largely interpretations of vague inner visceral sensations, tend to disappear; patients lose appetite, sexual desire, and so on.

12. (*a*) "[about the baby]. . . . It was an awful funny kind of feeling, kind of a hopeless feeling. . . . All gone. It was awful! Then you get sick to your stomach. Then when his eyes clear up and he starts to smile at you, that feeling goes."

(*b*) "When he was small, it's as if you are doing everything you know how to do, everything you can do. He'd get those colicky spells and he'd roar and scream, and I'd get that panicky feeling and I'd want to run."

(*c*) "I couldn't eat yesterday. After I got the supper on the table, I felt like I was choking. That first bite, when I got so hot. I had put the meal on the table and I sat down and started to eat, and I couldn't get it down. I just drink tea and bread and butter. I couldn't get anything down. When I get like that, I can't eat. If it wasn't for the children, I wouldn't care."

In the realm of speech behavior, it may be seen that the patient tends to express herself in a detached way when speaking of the depressed period; she talks in patterns, in generalizations, of remote events, and of other people. What comments she makes about herself tend to be the comments of the outside observer rather than of the inside one. Notice the difference in the pronouns and points of view in the first sample:

13. (*a*) "Of course he isn't talking or anything like that, but he's looking at me and smiling, and he's getting so he knows his name, and he shows recognition when his brother talks to him and his father and he's more friendly now, but when *they* are little they don't talk and *they* don't do anything, and *you* just take care of them, that's all."

(*b*) "I get a lonesome feeling . . . just like I'm in the house and there's nobody there all day, and I'm taking care of the baby, and he isn't gurgling the way he does now, and it seems awfully quiet, just as though you're all alone in the world."

(*c*) "I was sleepy and yet I couldn't sleep. I was just waiting for the baby to cry for the next feeding, and he'd be so fussy and he'd be crying, anyway you couldn't sleep. It was as though I wanted to sleep and needed the sleep, but I couldn't."

It was possible with this patient to follow the course of the illness both toward recovery and toward an exacerbation. She described in interview the manner in which a short vacation at her sister's home was followed by a quick recovery.

14. (*a*) "The doctor said to see if I could either get the baby out of the house or get myself out of the house, I'd be better off. So my sister took me to her home in Revere and I stayed there a week, and then I felt awful guilty. 'Why should my mother be taking care of the baby? After all, my mother's 74 years old.' I thought, 'Well, everybody else seems to be able to take care of their babies, and I should be home taking care of mine.' So I packed my bag and things and went home."

(*b*) "My mother went home, and I was edgy, sort of tense. Right away my husband started helping with the baby at night. . . . It took about two and one-half weeks, for then the capsules must have started to work, and I started to enjoy my food, and I could cook without getting sick, and the baby didn't seem to be such a problem. And by this time the baby was smiling and noticing things, and I wasn't so afraid of the baby."

In connection with coming into the hospital, there seemed to be a very quick reaction in a lessening of the severity of the illness. In the second interview, which followed the first by about 10 days, we find:

15. (*a*) "Well, things are going good now, the baby's big and I don't feel nervous with him, and it doesn't seem as if my husband bothers me so much. I don't know why. . . . Things just don't aggravate me. . . . This morning we had a flat tire, and I knew I was supposed to be here at about 10 minutes of 9, and I surprised myself, because any other time I would have got rattled, but I didn't get rattled today. . . . I didn't let it bother me."

The fact that this effect was in some measure a therapeutic one was supported by the upset which occurred before the third interview. In reviewing the period before the sudden reappearance of anxiety and depressive feelings, the patient said:

16. "And I was doing good. . . . But one thing, Saturday there was an income tax blank in the mail box. Every year we have a battle royal, and I told him to take care of the whole thing yourself. . . . He said, 'I hope you saved all the receipts from the hospital bill.' . . . He meant here. So I told him, I said, 'Up to the present time I haven't paid anything.' So he gave me a very, very dirty look, and he said, 'That sounds very fishy to me.' He thinks I'm doing something sneaky behind his back. . . . I guess I must have been very mad just the same. . . . I guess I was washing the dishes and making more noise than usual . . . and he said, 'You better watch out or you'll end up in Revere again.' . . . He shouldn't have said that to me, because I was trying hard to forget about it and what happened before."

In this third interview we find that she has become very emotional again; the emotion which she expresses is signaled by crying spells. But the patient's acute experience of emotional release is accomplished only vicariously—she is not able to be freely expressive about her own problem but only can weep for herself as she identifies with the frightened lost child who mourns for his mother.

17. (*a*) "I was afraid. I got the awful feeling just as if I did not know what was happening. [Crying] I don't know what will happen to my children. Every time I look at the baby—I wonder, I don't want anything to happen to me, 'cause I don't know what will happen to the two of them."

(*b*) "All that's on my mind is the two children. I told my mother I don't know what will happen to them if anything happens to me. She said not even to think about it, but the baby's so small. Every time I look at him [crying intensely] I don't know."

(*c*) "He's a nice baby and he's pretty and I want to take care of them. They're my children, but I'm so afraid of something happening to me. My mother's old, and she couldn't take care of them. What would happen to them? [intense crying] I don't care for myself; what's the difference? But I got to keep on going for them; they're too small."

The situation, that the experimental nature of the project made it possible for no fee to be charged, was explained to the patient, and she left appearing relieved. In a subsequent, unrecorded interview, the patient spent the entire time expressing with vigor many very hostile feelings about her husband. She described him as incompetent, lazy, stupid, opinionated, suspicious, etc., at great length. She was given another appointment after this interview, but she canceled it. When she was finally reached several weeks later, after a number of attempts had failed, she said that she had decided not to come any more because she was afraid of becoming too dependent upon the doctor. It is our impression that this reaction represents a defensive "flight into health" because of the patient's fear of the aggressive impulses so freely expressed in this fourth interview.

INTERPRETATION OF THIS MATERIAL

In the discussion which follows we are using the material which we have detailed above to describe the pathogenesis of a depression. The method of making inferences from a single case has always many disadvantages, in that it is impossible to know how general are the implications drawn; for this reason we can make no claim other than that this information is appropriate to this case.

This patient's relations to other people are primarily on the identification level, and these relationships are very ambivalent. We may say, if we try to understand what she says from a viewpoint inside her, that it is necessary for her to be accompanied to feel safe; we may almost say that to feel human, she needs to have a perceptual relation to a human being.* But we notice immediately that this sort of relation is more important from a general than from a particular standpoint; this patient derives a good deal of comfort from being simply a member of a crowd. She says her family were not close to each other, they did not talk intimately to each other about their problems; on the other hand, they were members of an urban community, and there were always signs of human life in the near vicinity. In her new home in the country she notices that she feels lonesome a good deal of the time; she is glad to see tradesmen, and recently she has noticed in herself a reaching out for companionship, as, for instance, in her attempt to continue a relationship developed in the maternity hospital with a fellow patient.

Further, we note that this patient has a great deal of difficulty with close emotional relationships; she is easily influenced to feel bad in a number of ways by the actions of other people, and this is especially true when the other people are specifically identified to her. The most acute example of this vulnerability we see in the case of the fellow patient upon whom the obstetrician was carrying out some form of rotation of the fetus; our patient felt stiff and paralyzed, and she was so upset that the feeling of distress was very severe. It is interesting here that our patient "felt into" the situation, both from the standpoint of the fellow patient who was being tortured and from that of the student nurse who was being horrified, but the point of view from which the doctor was proceeding was completely foreign to her.

In dealing with her husband she finds the same occurrences turning up time after time; she complains of her excessive vulnerability and compares herself unfavorably with her friends, who are not so sensitive to the behavior of their husbands. When her husband is sulky and refuses to speak to her or to discuss the reasons for not speaking, she takes it personally, even though she knows that it is not a function of any misbehavior on her part. Alienation from the husband leads to the same stiffening reaction noted so acutely in the former situation. This stiffening appears to be a general tensing of muscles in an attitude of chronic fearful expectation, somewhat in the manner of a passenger in an automobile who fears a wreck.

This patient tends to be at one or the other extreme of her relation to other people; in the case of husband and doctor, when the relationship is good she feels greatly supported, but when it is not she feels greatly threatened. The sequence in the relation to a therapist in this brief series of interviews was of especial interest here, since the first interview, although designed more as an exploratory one in the

*This same need was more dramatically evident in another patient, a young man with schizophrenic delusions and hallucinations. This patient described how the delusions always disappeared whenever he was talking to someone, only to reappear when he was again alone.

service of a research project, was followed by such a beneficial change in the patient's state of mind that she found herself much more tolerant of her husband. When, however, the relationship was disturbed by suspicions about the lack of a bill, the patient went back to a state of greater distress, with a reemergence of depressed, and even suicidal, ideas.

There is a very sharp contrast between the "frozen" immobilization related to being isolated and the "red-hot" temper which the patient displays at other times, notably in protecting her son. In her cleaning "sprees," she finds herself expressing destructive impulses with violence by attacking papers and dirt.

From this sequence of observations we may conclude that this patient demonstrates certain characteristic patterns of relationship with other human beings:

1. She is very dependent upon such a relationship and is blocked and uncomfortable when feeling alone or isolated.

2. The dependence is easily transferred, e. g., from husband and mother to sister in one case, from husband to doctor in another.

3. When the dependent relationship to superior persons is disturbed, the patient finds herself greatly inhibited in expressing feelings; but when the patient feels herself to be the responsible superior person, her freedom of expression is much greater: She can feel and act rather freely as long as she is protecting her son.

4. She can feel and act similarly somewhat freely in a situation where no other human being is involved, e. g., in tearing papers.

If we now look at the circumstances surrounding the birth of the second baby, we find that all of these considerations are involved in the onset of her depressive episode. The patient remembers two things particularly: She was very much aware of an "inhuman" quality to the baby, and she was preoccupied with the idea of something happening to him. The baby, to the patient, had the form of a human being, but not the "content"; he looked like a person but did not act like one; she knew him to be human, but he did not "feel" like it. We postulate, therefore, that the crucial problem in the relation of this woman to this baby was that she was desperately (albeit unconsciously) afraid of her own tendency to simplify her life by destroying this alien, "inhuman" intruder.

From the standpoint of the social system this simplification is the greatest possible danger. To restrain herself the patient needs help; i. e., she needs an affirmation of her own "humanness" in a relation to others. But the resentment toward her mother and husband make them unavailable as supports of this type. Regressively pushed backward then in development by the strain, the patient's conception of the group becomes that of a vague hostile force. To maintain "humanness" and to restrain her violence, she allies herself with this vaguely conceived group; but such an alliance implies the assumption of the hostile, critical attitude toward herself.

BREAKDOWN—STAGES IN THE REGRESSIVE PROCESS

In this patient we may discriminate three stages in the process from a state of compensation to one of severe decompensation. The stages which may be described are of considerable interest because of the correspondence to stages in the breakdown process in some experimental work to which we shall refer.

1. In the stage of compensation, we find this patient getting along in a tolerable way; at least she feels no inclination to seek medical help. She does her work

in a passable manner, keeps the house, does the cleaning and cooking, etc. In this phase she is oriented toward the task without being too much aware of the means; she has "her eye on the ball," so to speak. This sort of adaptation represents an uneasy fusion between the patient's own wishes and those of the group in which she finds herself. She would consciously, at any rate, prefer that her husband be a bit more affectionate and cooperative, but she gets along. The viewpoints of the patient and of her immediate group are in essential agreement about her task and her performance.

2. In the second stage, there is a growing awareness of her own inner sensations with feelings of loneliness, tiredness, anxiety, crankiness, edginess, etc. She is constantly under a strain in caring for the baby, but she is unable to complain or to ask her mother or husband to help, for fear of imposing upon them. We see, then, a woman surrounded by an increasingly hostile, demanding group, aware of severe feelings of anxiety and exhaustion, and tempted to let fly at the baby as a scapegoat. As the situation gets worse, even the nonhuman environment appears to become hostile, until the ceiling and the walls seem to be attacking and suffocating her.

3. In the third stage, the patient gives up; she becomes indifferent to the pressures which previously were so important to her; she accepts without demur the savagely critical opinions which she has been so desperately attempting to escape in the previous stage. She is no longer interested in the attempt to force approval from her group but accepts the role of a failure and lapses into depression.

It appears to us, here, that this is an effort by the patient to adopt a (paradoxically self-preservative and self-destructive) method of maintaining herself "in general," i. e., in relation to the group, while abandoning herself "in particular," i. e., as an egocentric narcissistic system. Her point of view is changed to agree with that of the hostile environment, and in the process she is alienated from her own feelings of distress. Having lost this connection, she is only very dimly aware of physiological needs: She cannot eat; she has difficulty sleeping; it is only with the greatest effort that she can do the bare minimum of work which is necessary to keep the house going. In this state she views herself with disapproval and disgust; she is remote and distant from herself; she appears like a thing, and the destructive impulses previously feared in relation to the baby are now feared in relation to herself.

The phasic changes in subjects in the experimental work reported by Bartlett [2] and by Davis [3] are closely similar to those noted here. In an experimental situation of operating a simulated aircraft over very long periods of time, they found that their subjects, all experienced pilots, carried on for a long time before beginning to show signs of strain. As the pilots began to have difficulty in maintaining performance, signs of breakdown occurred first in the integration and timing of sequential reactions, and a "growing dominance of the proprioceptive aspects of the situation" became prominent. Bartlett described in the acute experiment in the "skill-tired" subject three classes of observations: 1. The pilots became less reliable and gave false reports; they tended to blame the operator for their own failures. 2. The awareness of physical discomfort increased a great deal. 3. The subjects became very irritable. In our patient we note a growing fear of unreliability in herself, hostile feelings toward her husband as the source of her discomfort, a variety of uncomfortable feelings associated with anxiety and fatigue, and "cranki-

ness." After this period a further stage occurred in which some pilots showed a "withdrawal" reaction; they became indifferent to many signs of danger. It is of particular interest to notice the comments made by these investigators to the effect that in the "overactivity" reaction the pilots frequently improved their performances in response to intervention by the experimenter, but, on the other hand, the pilots in the "withdrawal" reaction were much more difficult to influence.†

The point which we wish to emphasize in the similarity between the clinical and the experimental observation is the regressive development from (1) a task orientation to (2) an egocentric orientation, with many pressing interoceptive and proprioceptive sensations, to (3) an eventual state of indifference and self-abandonment. Depending upon the individual, the self-abandonment may be either passive, with a feeling of giving up, or active, with suicidal tendencies.

GOOD AND BAD OBJECT IN PERSONALITY DEVELOPMENT

We have been particularly struck in the material quoted above, by the manner in which the patient was unable to appreciate the newborn baby as human. It was not until the baby was able to respond to her in a predictable, patterned way (i. e., by smiling, gurgling, etc.) that she could feel he was a "person."

It is of great interest to note three different attitudes of this mother in relation to this baby at various stages in the developmental process. First, we find that the most gratifying situation to the mother (and, we guess, also to the child) is the relation established when the child is able to respond and the mother can feel warmed and pleased by his response: To her at this time the child is very clearly a "good object," in the sense of a gratifying human relationship. A second type of relation is demonstrated by her descriptions of the first three months, during which time the baby was demanding, cranky, rejecting, and frightening in various ways: This attitude on her part is appropriate to the apprehension of the child as a "bad object." Third, when she becomes really depressed and apathetic, the baby almost ceases to exist as an important consideration, and we may say that (for theoretical purposes, since it is always necessary to exaggerate in order to make a distinction clear) the baby practically ceases to exist as a tangible outside human being.

These three stages of relation to the baby are identical with the three stages described above, with the difference in viewpoint as the only important distinction: The "good object" stage is that of adaptation; the "bad object" stage is that of increasing distress and increasing dominance of the proprioceptive aspects of the situation, and the third stage, that of depression and loss of the object, is a stage of withdrawal and indifference. We believe that it is possible to trace these same three stages through the early development of a child and to find in the course of this tracing various important implications for the understanding of the pathogenesis of several types of emotional illness.

In this developmental sequence, and this is the point so well demonstrated by this patient, there is a crucial reorientation which must take place before a

† In the terms of this discussion, we propose that the most important aspect of the change from the aggressive to the withdrawn state is the regressive shift from a relation to the contemporary group, in the former state, to a relation to (the memory of) an early undifferentiated group, in the latter. Channels of communication remain more utilizable in the aggressive than in the withdrawn condition.

child becomes a responsible civilized adult. This orientation may be described as a shift from a narcissistic to a maturer point of view, but for the purposes of this discussion we propose to describe it in a somewhat different way, with a view to being able more clearly to see some of the mechanisms involved. Thus, we describe this orientation as essentially from a prehuman to a human point of view. It is possible further to locate this reorientation in the developmental sequence, again with the proviso that any such localization depends upon a "black-white" dichotomization which is only abstractly related to the kaleidoscopic shifts in process which are to be seen in the specific example. In this manner, the transition from prehuman to human orientation is equivalent to a transition from preverbal to verbal methods of communication and depends upon the development of language skills. This is a clear relation, it seems to us: The prehumanly oriented baby does not have to use language to get what he wants, since it is the function of the mother to care for and to anticipate the needs of the baby. As it has often been noted, in human beings this function of the mother is essentially an extension of the symbiotic state of affairs which occurs in utero. Thus, the development of language and methods of communicating with a wider group are events which (1) are made possible by the increasing growth and somatic maturation of the baby and (2) are made necessary by the decreasing willingness of the mother to continue to supply every need before it is experienced by the child.

The two end-points in this sequence may be defined with ease. On the one hand is the baby, who wakens when hungry and goes back to sleep when fed, without any demonstrable concern with the method or agent by means of which he is fed; and, on the other, there is the fully mature adult, who operates always in relation to his social system, habitually denying himself immediate (instinctual) gratifications in favor of group values, according to the reality principle. The steps in the shift from the one to the other of these end-points are of crucial importance in understanding the process, and we hope to be able to clarify some of these stages. Since it is impossible to get any verbal report from the preverbal period of human development, we propose to describe the sequence of events in behavioral terms and draw inferences from the behavior.

In the process of birth the newborn baby becomes actively related to air as the initial external substance. The behavior of suckling is the method by means of which a relationship to a human object is first set up.

In the newborn baby, the alternation of sleeping and waking demonstrates a behavioral shift between minimal and maximal activity, and the first discrimination which is demonstrated by this cycle is that of separating a state of danger (primary anxiety) [4] from a state of peacefulness. The observer is aware of the difference in these states, even though it is not possible to say that the baby is: The baby's behavior is meaningful to the observer long before it can be meaningful to himself.

With the development of the suckling reflex and the beginning of a feeding history, the baby develops a skilled relation to a part of a human being, and we may assume that for a long time he is pretty much exclusively concerned with this aspect of the world, and not much else. But the situation immediately becomes somewhat complicated, we infer, by the fact that in this first part-object discrimination the child becomes related to an entity in such a way that he acts upon, and derives sensation from, the entity when it is present and, on the other hand, in some way learns to project in an anticipatory way the image of the part-object

when it is absent. The child develops two different types of experience in relation to the entity, on the one hand a close proprioceptive, muscular, visceral, and gustatory relation to the present object (breast or nipple), and, on the other hand, a distant ("imaginary" or hallucinatory) relation to the absent object.

Now it appears to us that to understand the situation adequately at this point we need to refer to a salient feature in the early development of mentation, i. e., the difficulty in the understanding of process, even though the two end-stages may be perfectly clear to the individual involved. A child, for instance, may demonstrate very great dissatisfaction when deprived of a toy, but immediately after getting it back he may lose interest in it entirely; it is a very long time before he becomes able to plan not to be deprived of, or to be able to experience, the relation to the human object who is important to him in getting what he wants. In the case in point here, we believe that this general characteristic of human behavior implies that the baby is aware of the present object and the absent object as two entirely different entities in discontinuous display, rather than as complementary aspects of a single entity bound together in a continuous existence.

In the very earliest period of life the value to the infant of the fostering adult (the "anaclitic object") [5] in the experience of the baby is primarily that of providing the baby with an opportunity for useful activity; on the contrary, in the absence of such an attendant, the baby suffers from helplessness and displays relatively random and violent behavior. In the two cases, by means of observation of the expression of the baby and by analogy to feelings of adults when exhibiting similar facial expressions, we assume that the former experience is relieving, the latter distressing.

But there appears to be a paradoxical situation here, in that the baby in the former case seems to be oblivious of everything except the action (e. g., suckling) in progress at the moment, whereas in the latter case the baby seems to be much more clearly aware of the environment. As the baby develops, he becomes able to display the relief reaction with less and less contact with the attendant; we may say, then, that the growth of experience is measured by the manner in which the baby becomes more and more able to predict a relation to an object by means of more and more distant data. This is another way of saying that the baby becomes more and more able to integrate into one concept the two ideas of the present and absent object.

In the early period of childhood it is apparent that the bad human object is the absent attendant; in the continued absence of such a person, the baby will not be able to survive. The absence of the attendant is the danger situation, the problem which is presented urgently to the baby for his solution if he is to continue his existence.

If we assume that the baby is totally devoid of sophistication and almost entirely limited in his ability to test reality, we can guess that to the baby the inner state of unrest (helplessness) which occurs when unattended is much more prominent than is the state of inner peace which occurs in sleep, and in the state of goal-directed activity present in the suckling experience. The peaceful, active state poses no adaptive problem, but, on the other hand, the painful state of random activity represents a pressing adaptive problem.

In the painful state, the attendant is represented by a hallucinatory image, and it seems reasonable to guess that (1) this image is relatively prominent, (2) it

seems to be the source of, and to be responsible for, the distress, and (3) this image is very vaguely identified. We should guess that in this latter situation, at any rate for the first few days of life, the child reacts to some very general ways of being helped or cared for with no possible awareness of the identity of the attendant.

The baby begins mentation by separating his world into polar antitheses which are classified as (1) "good," i. e., those situations imposing no strain upon the adaptive capacities of the baby, and (2) "bad," the stressful situations. Behavior in the pleasant situations quickly and easily becomes habitual and skillful, closely related as it is to reflexes which are easily trained; it then tends to become a part of the unconscious background of the baby's existence. On the other hand, behavior in the unpleasant situations is random to begin with and has to be organized in relation to an anticipated event rather than in relation to an immediate reality. To us, then, it seems that the development of thinking and planning must be more closely related to the bad object than to the good; we may say that, as necessity is the mother of invention, so the bad object is the mother of intelligence.

In the continued development of the child, the bad-object role, it appears to us, is played in the next act by the attendant adult involved when restrictions begin to be imposed upon the behavior of the baby. The bad object is now more complicated, in that it includes elements of absence (i. e., sensations of loneliness and distress associated with an unavailable attendant) and also elements of prohibition and active frustration by the attendant when present. In the development of a reality relation to the social system, this shift in the role of the attendant must be of very great importance in the development of the idea of a whole object. The prohibiting parent is much more apparent to the child than is the giving parent; the latter is taken for granted, the former, again, is an adaptive problem.

Up to this point we have tried to refer to the parental figure(s) for the most part by the ambiguous term "attendant," to indicate our belief that the human beings related to the child tend to be very vaguely discriminated and very nonspecifically identified. In the development which we suggest follows the two stages discussed above, the parental figures tend to become more clearly identified; this stage of development we see as the shift from a "dyadic" to a "triadic" relation, in that the child becomes aware of the existence of two attendant figures.‡

It is our impression that although skills, such as the baby develops in sequence as he grows, are learned with increasing increments of adeptness in the control of muscular movements, on the other hand, those parts of experience dealing with the large entities of the baby's world which will eventually make up the content of the person's mentation are separated out by a progressive differentiation by dichotomization. In this manner the first differentiation, as we noted above, is that between peace and chaos (primary anxiety); the second major differentiation takes place with the emergence of vague human images as the important variables. It goes without saying, of course, that this process is in itself immensely complicated.

Each successive step complicates the possibility of the experience of the child. The first step, the occurrence of the chaotic reaction related to unbearable sensations at birth, divides the world into two parts; the next step adds another possi-

‡ The baby certainly reacts specifically to the mother long before he can identify her in any symbolic way, but this is a different problem than that of "knowing" in mentation. The dog or cat reacts specifically without any symbolic "knowing" process taking place.

bility, with the relating of everything to a human object—here the baby can separate the waking period into a phase of distress and a phase of relieving of distress. In the increasingly sophisticated experience of the early "triadic" phase we find a further complication, in that with the emergence of two attendant figures from the background the child is presented with many more problems of adaptation and of understanding. Instead of the presence or absence of an attendant and the subsequent possibility of the punitive or gratifying behavior of the attendant, the child now has to deal with the presence or absence of, and the punitive or gratifying behavior of, both a mother and a father.

We find in the stage of development with which we are concerned here a number of implications of immense importance from the standpoint of a curiosity about the emergence of mentation in the child. In the first place, human beings are very much more capable of making value judgments on a comparative than on an absolute basis.[6] In the phases of existence prior to the triadic stage, the child, vaguely dealing with "attendant," has no standard of reference; he exhibits to the observer sharply differentiated reactions to the present and the absent attendant, but to the child's awareness these are discontinuous entities, rather than aspects of a single entity. It is only when he can discriminate two objects in the immediate present that he becomes able to compare and contrast various aspects of his experience with human beings.

In this comparison it is inevitable that each child will have a somewhat different experience because of the differing character of the two attendant parental figures; related closely to the differences in the parents will be the child's idea of himself, of his status and possible role behavior. But from a general, theoretical standpoint, it is possible to note certain implications of the process of differentiation as it affects members of this culture. In this way, as the father and mother figures are separated out from "attendant," there occurs a period of confusion, in which we guess that the fantasies of bisexuality are rooted; the child has to make a very large series of judgments, which can be put in adult language by some such statement as, "This particular type of behavior is carried out by the person having this particular type of genital organs." Where the relation to the parents is such as to discourage exploration into the various aspects of the situation, the development of the child will be hampered.

In this culture, it appears to us that the father is the natural heir to the "bad-object" role in the early stage of triadic development; he qualifies on several counts; he is more remote and unfamiliar; he is a natural competitor for the attention of the mother, and (in this culture, at least from a public standpoint) he is the authority figure, the accepted, normatively defined head of the household. As the father emerges, then, we assume that he becomes the more feared and hated parent; the mother, on the other hand, shines by contrast. Much of what he forbids she allows; what he takes, she gives, etc. As this process goes on, we propose that the mother figure becomes more and more apparent as a good object, and this is for the first time the occasion for the child to be consciously aware that an agent is operative in making for his comfort. Prior to the definition of the father the child deals with a situation of being pleased or displeased by "attendant"; subsequently, the possibility of being more or less pleased by the father or the mother occurs.

In the shift from the dyadic, attendant-child relation to the triadic, father-mother-child relation, and the social, group-individual relation, the person has to cope with the problem of a major shift in all of his value judgments. To the baby the father as a competitor and as a repressive punitive figure must be unambiguously "bad"; but to the child who wishes to become integrated into his group, it eventually becomes apparent that he must adopt the values represented by the father as authority figure: The father is the embodiment of the group norm. In addition, in varying degree, the immediate gratification of impulse and the permissive attitude of the early attendant figure come to represent a danger in that the (instinctual) gratification is followed by punishment of some sort.

Thus, the "good" and "bad" objects of the earlier stage come to carry opposite values; what is good to the narcissistic egocentric baby is bad to the socialized child. The child, in his group, very early begins to function as a representative of the group norm, rejecting and punishing with great intensity the erring member, frequently quite ignoring the examples of his own behavior which class him with the outcast.

We may now attempt to specify what it is that appears to us to characterize the person in a depression as we may relate the illness to the stage of development here. We propose that such an illness takes origin just at the stage wherein the child is in the process of making the shift in viewpoint from egocentric to social orientation. It seems to us that the depressed person expresses the hostile rejecting attitude of the group toward the erring individual, himself. He is caught in the attempt to retain his relation to a vaguely defined hostile group by agreeing with them in their punitive attitude, even in relation to himself.

If we refer back here to the clinical material cited above, we find that in the second phase of the regressive process the patient is aware of the husband and the mother as two separate demanding people toward whom she feels a great deal of resentment, even though she cannot express this resentment overtly in such a way as to relieve herself, or even so as to enlist their help; at the same time, the baby is dangerous and alien, rather, another hostile member of the group. All three are clearly identified and differentiated one from another, and each imposes demands upon her of a social nature. In the sudden collapse which ushers in the third stage, the group loses its individual members, and she displays an attitude which we assume to be her reactivated version of the hostile attitude of the group which she experienced, as a very young child, in her first efforts to adapt herself to a social existence.

In her recovery, she was taken in by her sister and pampered in such a manner as to gratify very completely the dependent needs for comfort, rest, and sleep which she was unable to obtain at home. The patient's recovery from the intense depressed phase was dramatic; in a week she was able again to become related to the group in a much more adult and discriminating way by the guilty feelings which she began to have at deserting her job; in this state of mind she returned home and began to care for the house again. The recovery process, set in motion by the reestablishment of a warm relation to a single, identified human being, her sister, was fostered upon her return home by the manner in which the baby in his fourth month began to react to her in such a way as to make her feel recognized and gratified. In the experience with the therapist, the patient noticed immediately after the first interview (in which she poured out her story in a remarkably compre-

hensive manner) that she was insulated against many of her husband's actions which previously had irritated her so much. But when the relation to the therapist was threatened by her suspicions as to what the absence of a bill might imply, she again developed a strongly depressively colored reaction in her crying spells and self-abandonment: "What happens to me doesn't matter; I am crying for my babies, who will have no mother if I die." § Further, with the restoration of the relation to the therapist she responded with relief, but the consequence of this relief and of the permissiveness of the therapist was such an extraordinary blast of hostility toward the husband that the therapeutic relation became too threatening and she had to quit, with the statement that she was afraid of becoming dependent; in other words, she was afraid of the flood of hostility which overran her when she was allowed to express anything she wished to.

It seems important to us to emphasize here the vague nature of the important figures in this woman's experience. It is common to say that the depressive illness is most importantly connected to the relationship with the mother, but it seems more precise to say that it is connected with the "attendant" or "anaclitic object"; either term implies that to the child the mother as a separate identified human being has not yet become clear. To this patient it seems to be immaterial whether the support received comes from her sister or from the male therapist: The more important aspect is the type of support available to her. The relationship between her visit to the therapist and her immediate relief was an observation which she could describe but was, as far as could be noted, entirely outside her area of clear, conceptual cause-and-effect thinking. Further, we can notice the implication that to her the behavior of various role-occupants is fixed within relatively narrow limits, since it seems likely that the "reality" aspect of the free treatment was at one and the same time a prominent factor in encouraging a dependent relation and a factor which (being outside her experience of doctors) made her frightened and suspicious when she reviewed the intensity of her attack upon her husband. To this patient the free and permissive attention of the therapist must have been a seductive situation in which she felt led on to an intense antisocial discharge of hatred toward her husband.

In examining the shift between depression and relief which we see in the material presented by this patient, there is at least one further item which seems to us worthy of comment: This is the very nearly categorical nature of the transition. Up to a point she hangs on with all her might, but when she lets go, she lets go all at once. The shift in the therapeutic relationship was similarly categorical. In both instances the good object appears to turn into the bad with dramatic suddenness. We believe that this "either-or" characteristic is importantly related to the early stage of conceptualization in which we have postulated this woman became fixated in her childhood. Her images of others tend to be valued not as more or less satisfactory, but, rather, as categorically good or bad. We suspect that in a more fortunate child the process of giving up the primal good object is more gradual, with the opportunity for protracted grieving of bearable intensity, as more and more of the blissful anaclitic relationship is taken away in the process of growing up. Where the reversal in value judgments takes place too early or too suddenly, the immense adaptive strain imposed makes for a break in continuity of the indi-

§ Even here we note the patient requires the help of the idea of her babies to express her own feeling: She can only be expressive vicariously.

vidual's own self-awareness; the resultant inability to remember the former state appears to us to be the essence of the process of repression.

Finally, it appears to us that there must be a very important connection between these events and the processes of sensation. The anaclitic relation to the primal object is a close, warm, supported type of relatedness, information about which is signaled to the baby via tactile, visceral, and proprioceptive channels; for the most part, the anaclitic object is associated with inner sensations, and we are convinced that this association has an important relation to the relative dimness of this object as a part of conscious experience. On the other hand, the admonitions from the group representative are apprehended largely by visual and auditory means; the authority figure is very much more clearly defined by "projicient" modalities,[7] and, we guess, is always clearer to the individual. In the regressive process, attention is shifted from less clearly defined, positively related objects to more clearly defined, negatively related ones, and to save himself the depressed patient deserts to the enemy.

This maneuver, in the characteristic manner in which the defensive operations of the personality frequently function, leads to the development of an illness of very great discomfort; but, on the other hand, this illness is one in which the patient maintains to a great extent the essentially human characteristic of thinking and language function. It appears possible that the major difference in the pathogenesis of depression and of schizophrenia in this frame of reference is to be found in the regression of the depressed patient to an early stage of group relatedness, and in the regression of the schizophrenic patient to the preconceptual concretistic type of mentation, which is the prevailing mode prior to the beginning of integration into the group.

SUMMARY

We have attempted to describe a brief depressive episode as a manifestation of major changes taking place in the relational field of which the patient experienced herself as a part. We have emphasized "field" rather than "individual," in analogy to modern theories in physics.

In these terms, the patient, under the impact of a series of changes in her social orbit, or field of relationships, suffers a disintegration and reinstates (in a regressive process) in the present moment a field appropriate to the point of the beginning of the development of language. In this patient reintegration could be observed to take place very rapidly in a situation in which the field presented support rather than strain.

REFERENCES

1. Frank, L. K.: Symposium on Genetic Psychology: Genetic Psychology and Its Prospects, Am. J. Orthopsychiat. **21**:506-522, 1951.

2. Bartlett, F. C.: Fatigue Following Highly Skilled Work, Proc. Roy. Soc., London, s. B **131**:247-257, 1943.

3. Davis, D. R.: Disorders of Skill, Proc. Roy. Soc. Med., **40**:583-584, 1947.

4. Freud, S.: Problem of Anxiety, New York, W. W. Norton & Company, Inc., 1936.

5. Shands, H. C.: Anxiety, Anaclitic Object, and Sign Function, Am. J. Orthopsychiat. **24**:84-97, 1954.

6. Bartlett, F.: The Mind at Work and Play, Boston, The Beacon Press, 1951.

7. Sherrington, Sir C. S.: Integrative Action of the Nervous System, New Haven, Conn., Yale University Press, 1948.

CORTICAL REPRESENTATION AND FUNCTIONAL SIGNIFICANCE OF THE CORTICOMOTONEURONAL SYSTEM

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STOCKHOLM

EXPERIMENTS by Adrian and Moruzzi [1] on the activity in the pyramidal tract of the cat indicated that in this animal the functional link between the pyramidal and the spinal motoneurones is not simple. In experiments on the same animal, Lloyd [24] showed that there is a complex relay system at the segmental level between the pyramidal fibers and the spinal motoneurones in the lumbar region. He found no evidence that the spinal motoneurones in the lumbar region of the cat are directly influenced by descending volleys in the pyramidal fibers, and this conclusion is in accordance with the histological findings of Szentágothai-Schimert.[34] In experiments on cats, we confirmed Lloyd's observation and found that pyramidal activation of the motoneurones in the cervical region of the same animal was also of internuncial order.

On the basis of electromyographic studies in monkeys, Cooper and Denny-Brown * concluded that in this animal there is a close relationship between the corticospinal neurones and the motoneurones. Hoff [18] and, later, Hoff and Hoff,[19] using bouton degeneration, studied the terminations of the corticospinal neurones in monkeys (Macacus mulattus) and found that extirpation of Area 4 was followed by degeneration of terminals on the spinal motoneurones. Only recently has functional evidence been presented by Bernhard, Bohm, and Petersén † and Bernhard and Bohm [4] for a direct activation of the spinal motoneurones by descending volleys in corticospinal fibers in the monkey. That fraction of the cortical system, the descending volley which activates the spinal motoneurones directly, i. e., monosynaptically, we refer to as the corticomotoneuronal system, or the CM system. The present investigation deals with the cortical representation of the CM system for different muscles and its functional significance.

METHODS

The experiments were carried out on monkeys (Macacus mulattus) with light pentobarbital (Nembutal) anesthesia, and small doses of tubocurarine U. S. P. were administered. The animal was placed on a heated table and kept on artificial respiration. The skull was mounted in the stand of a stereotactic instrument, and the spine and legs were fixed by means of clamps and bone drills. The exposed parts of the cortex, spinal cord, and nerves were covered with liquid petrola-

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* References 11 and 12.

† References 2 and 3.

tum U. S. P. (38 C.). The rectal temperature, as well as the temperature of the liquid petrolatum pools, was kept constant at 38 C. Square-wave electrical shocks (duration 0.2 to 1 msec.) of different frequencies were used for cortical stimulation. The action potentials were led off from different forelimb nerves to a differential amplifier and recorded with an oscillograph. Monopolar stimulation was used, the stimulating silver-wire electrode having a tip of about 0.5 mm. The cortical activity was recorded by leading off the EEG from the frontal, precentral, and postcentral areas on the stimulated side.

RESULTS

A. General Characteristics of the Monosynaptic Response to Cortical Stimulation

Figure 1 shows the general shape of the electrical response in a forelimb nerve to contralateral cortical stimulation at a frequency of 20 per second. The stimulating electrode was placed within the forelimb subdivision of the precentral area and the recording electrodes on N. radialis. The records (*A* to *D*), taken at various intervals after the beginning of the repetitive stimulation, show a series of superimposed records of the action potentials following upon each cortical stimulus. One second after the beginning of the repetitive stimulation (Fig. 1*A*) each shock elicits a late response, having a latency of about 5.5 msec. During the following seconds an early response appears, the amplitude of which increases (Fig. 1*B* and *C*) to a maximum. Later on the early response decreases (Fig. 1*D*), and usually it disappears in order to appear again. These fluctuations of the amplitude are typical for the early response when it is led off from nerves or ventral roots innervating forelimb and hindlimb muscles.

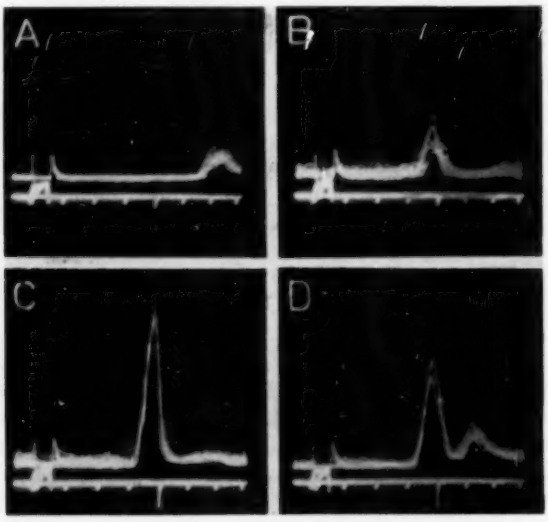


Fig. 1.—Superimposed action potentials in the left radial nerve following each stimulus in a train of shocks (stimulation frequency 20 per second) delivered to the forelimb subdivision of the right precentral area. *A*, at the beginning of stimulation; *B*, *C*, and D at two, three, and four seconds, respectively, after the beginning of stimulation. Time in milliseconds.

In different types of experiments ‡ it was shown that the early response, which in this experiment had a latency of 3.2 msec. (Fig. 1*B* to *D*), represents activity

‡ References 2 through 4.

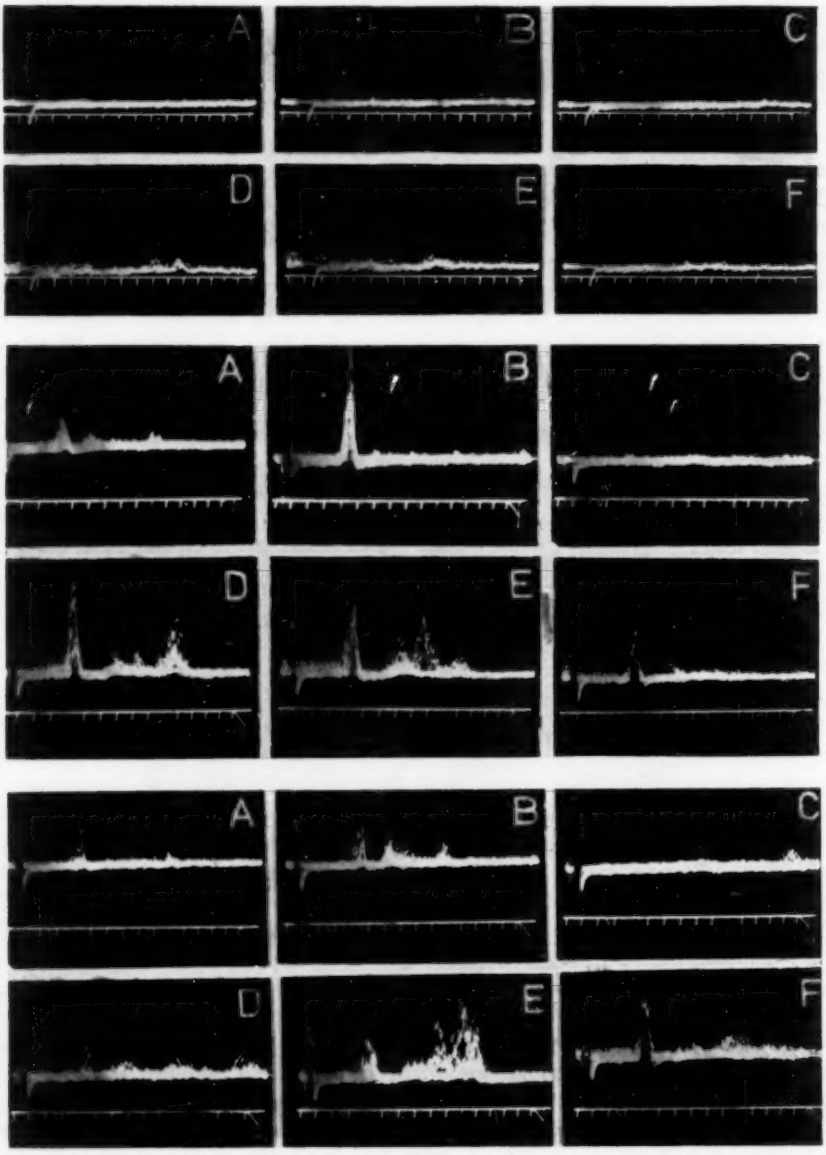
in motoneurones which are monosynaptically activated by descending volleys in the corticospinal neurones. According to our earlier investigations, this corticomotoneuronal system, the CM system, comprises the corticospinal fibers with highest conduction rate, i. e., about 70 meters per second, corresponding to the diameter values of about 12 to 14 μ given by Häggqvist [17] and Lassek.[20]

Our earlier investigations showed that the monosynaptic response is generally more pronounced in the forelimb nerves than in the hind limb nerves, and it was always found that the late responses dominate the records obtained from hind limb nerves. As expected, the size of the different responses to contralateral cortical stimulation was found to be dependent on the narcotic level. When the narcosis was deepened, the responses in the hind leg nerves always disappeared before those in the forelimb nerves. In the experiments published in this paper, tubocurarine was given in order to prevent muscle contractions. Thus the responses described appear in preparations in which there is no proprioceptive inflow due to muscular contractions.

In preliminary mapping experiments [2] we found that the monosynaptic responses in the motoneurones innervating hind leg muscles could be elicited from the cortical hind leg subdivision only, whereas stimulation of the cortical forelimb subdivision gave monosynaptic responses in the forelimb nerves. We have now attacked the problem concerning the topography of the cortical representation of the CM system for different muscles, and we have first chosen two antagonistic forelimb muscles, namely, the triceps and biceps muscles.

Since (1) it was found that repetitive stimulation had to be used for the elicitation of the monosynaptic response [3] and (2) the different phases of the amplitude fluctuations during repetitive stimulation behaved differently at different frequencies, an introductory series of experiments was performed in order to select the most convenient frequency for the mapping experiments. Shocks of short duration were used (less than 1 msec.), and frequencies between 1 and 35 per second were tested. The records in Figures 2, 3, and 4 show the behavior of the responses in the triceps nerve at the stimulation frequencies of 13, 25, and 30 per second. In Figure 1, and in the following figures, each portion (*A* to *D*) shows a series of superimposed records taken at different intervals after the beginning of the repetitive stimulation. In Figures 2 to 4, the records *A* to *F* were taken 1, 2, 3, 8, 9, and 10 seconds after the beginning of repetitive cortical stimulation of that part of the contralateral forelimb subdivision within which the lowest thresholds for the monosynaptic response in the triceps nerve were obtained. In this type of experiment the stimulus strength was slightly supraliminal for monosynaptic response at the stimulation frequency of 20 to 25 per second (below). When recording from the triceps nerve, we never found any monosynaptic response to single cortical stimulation. Actually, with the technical arrangements described, frequencies below 10 per second did not give any response during the first 20 seconds of stimulation.

We avoided the use of longer stimulation periods because of the cortical disturbances which appear after such stimulation. In this connection, it should be pointed out that in the following mapping experiments we used as short stimulation periods as possible, and in all experiments the normality of the cortical activity after the stimulation periods was controlled with simultaneous EEG recordings.



Figs. 2, 3, and 4 (upper, middle, and lower sections).—Records obtained by leading off from the triceps nerve (*A*) 1, (*B*) 2, (*C*) 3, (*D*) 8, (*E*) 9, and (*F*) 10 seconds after the beginning of the repetitive contralateral cortical stimulation with frequencies of 13 per second (Fig. 2), 25 per second (Fig. 3), and 30 per second (Fig. 4). Time in milliseconds.

From a comparison of Figures 2, 3, and 4 it is evident that the monosynaptic response (latency in this case about 3.4 msec.) was most pronounced when a stimulation frequency of 25 per second was used. In Figure *2D* and *E*, obtained eight and nine seconds after the beginning of the repetitive stimulation with a stimulus frequency of 13 per second, there was only a trace of the late responses (7 to 9 msec. after the shock artifacts), and no monosynaptic response. At the stimulation frequency of 25 per second, the monosynaptic response appeared during the first second after the beginning of the stimulation (Fig. 3*A*). There was an increase to maximal amplitude (Fig. 3*B*) during the next second, followed by a decrease of the amplitude to zero (Fig. 3*C*). In Figure 3 records *D* to *F* illustrate the second phase of augmentation and fall of the monosynaptic response. In Figure 4, obtained at a stimulus frequency of 30 per second, the amplitude of the monosynaptic response was much less than in Figure 3, both in the first (Fig. 4*B*) and in the second (Fig. 4 *D* to *F*) phase.

The phasic amplitude variations of the monosynaptic triceps nerve response to cortical stimulation with seven different stimulation frequencies, obtained in a similar experiment, are illustrated graphically in Figure 5. The amplitude values are plotted in per cent of the highest amplitude value obtained, which happened to be the maximal value during the first phase at the stimulus frequency of 25 per second. Time from the beginning of the repetitive stimulation is given on the horizontal axis. The diagram shows that the latency of the building up of the first phase shortens from about eight seconds (at 13 per second) to one second (at 25 per second) in order to increase again at a higher stimulation frequency (35 per second). In parallel to this regular shift in the delay of the first phase, there is a regular variation of the amplitude of the first phase. Thus, the amplitude of the first phase increased when the stimulus frequency was increased from 13 to 25 per second but fell again at higher frequencies. Thus, when repetitive cortical stimulation was used, the response began to build up at a stimulation frequency above 10 per second. When the stimulation frequency was increased to 20 to 25 per second, the "building-up rate" increased progressively, and the monosynaptic responses also reached higher maximal values. The subsequent decrease in the amplitude was also most rapid at the stimulation frequencies of 20 to 25 per second.

The behavior of the first phase of the monosynaptic amplitude fluctuations at different stimulation frequencies is graphically illustrated in Figure 6. The maximal amplitude of the monosynaptic response in the triceps nerve during the first phase (filled circles), as well as the latency of the first phase (open circles), is plotted against the different frequencies tested. The amplitude values are given in per cent of the maximal value obtained, and the latencies are given in seconds (both on the vertical axis). As seen, the shortest latency of the first phase, as well as the highest amplitude of the monosynaptic response during this phase, was obtained at frequencies of about 25 per second. A further discussion of the phasic fluctuation of the amplitude of the monosynaptic response will be postponed until after the presentation of the different mapping experiments. In this connection, it should only be pointed out that from the experiments described a stimulus frequency of 20 to 25 per second is most convenient for the mapping experiments because these stimulation frequencies are the most effective for the building up of the monosynaptic response, as shown by the short latency and high amplitude of the first phase of

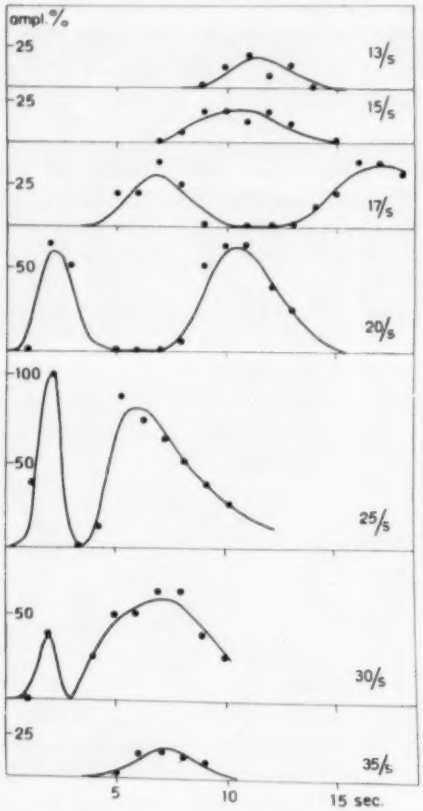


Fig. 5.—Amplitude values of the monosynaptic response in the triceps nerve to contralateral cortical stimulation with different frequencies (13, 15, 17, 20, 25, 30, and 35 per second) plotted against time from the beginning of the repetitive cortical stimulation. The amplitude values are given in per cent of the highest value obtained (100% in curve with a frequency of 25 per second).

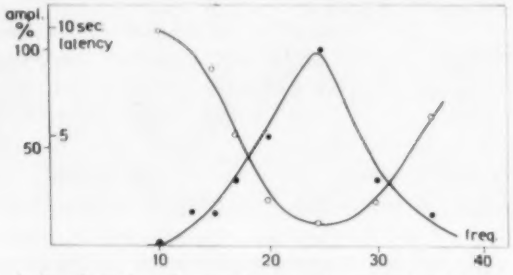


Fig. 6.—Filled circles, latencies (in seconds on the vertical axis) of the first phase of the building up of the monosynaptic triceps nerve response to contralateral cortical stimulation, with different stimulation frequencies plotted against the different stimulation frequencies tested. Open circles, maximal amplitude values during the first phase of the monosynaptic triceps response (in per cent of highest value obtained on the vertical axis) plotted against the different stimulation frequencies tested.

the monosynaptic amplitude fluctuations during repetitive stimulation. Experiments were also performed in which the effect of different stimulus strengths was tested at different frequencies, and they gave the same results.

B. Characteristics of the Monosynaptic Response in Different Nerves in Relation to the Extension of the Contralateral Cortical Field Stimulated

1. *Cortical Representation of the CM System for the Triceps Nerve.*—Experiments were performed in which the action potentials were led off from the triceps nerve when different points within the precentral cortical area were stimulated. Because of the findings in the experiments described above, a stimulation frequency of 25 per second was used with a shock duration of less than 1 msec. Figure 7 shows the surface of the precentral cortical area from a typical experiment, and the different points numbered indicate the different sites on the cortical surface on which the stimulating electrode was placed. The points were tested in the order given by the numbers (1 to 21). The diagrams in Figure 8 show the amplitude

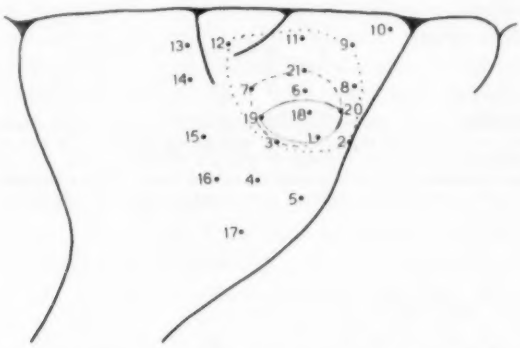


Fig. 7.—Map of the precentral area and the orientation of the different points (*1* to *21*) stimulated in the experiment described in the text, in which the responses were recorded from the contralateral triceps nerve (stimulation frequency 25 per second). Circle drawn in full, one-second latency field; dashed circle, three-second latency field, and dotted circle, seven-second latency field. For further explanation see text.

values of the monosynaptic triceps nerve responses (vertical axis) at different intervals after the beginning of the repetitive stimulation (horizontal axis), when the Points *1*, *21*, and *5* were stimulated. The curves drawn in full thus illustrate the amplitude fluctuations of the monosynaptic response in the same way as in Figure 5 (25 per second). The building up of the monosynaptic response during the stimulation period was most rapid when Point *1* was stimulated, in which case it appeared one second, and reached maximum three seconds, after the beginning of the repetitive stimulation. The latency of the first phase was three seconds when Point *21*, and eight seconds when Point *5*, was stimulated. The amplitude value of the monosynaptic response during the first phase was also highest when Point *1* was stimulated. Similar curves were drawn on the basis of the results obtained when the different points (*1* to *21* in Fig. 7) were stimulated in the same manner. The latencies of the first phase of the different curves were then measured. It was found that the monosynaptic response to stimulation of Points *1*, *18*, *19*, and

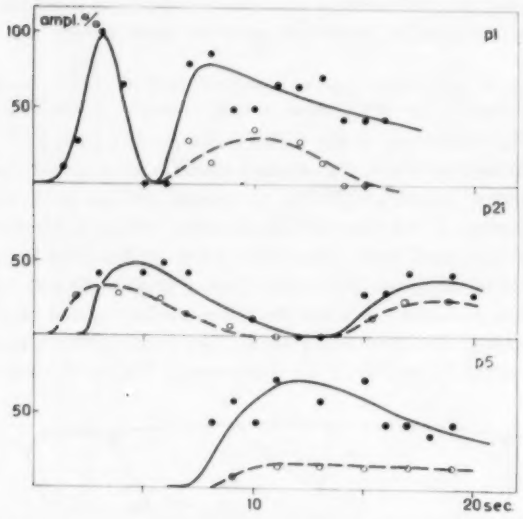


Fig. 8.—Filled circles (curve drawn in full), amplitude values of the monosynaptic response in the triceps nerve to contralateral repetitive cortical stimulation (25 per second) applied at different cortical points (*1, 21,* and *5*; see map in Fig. *7*), plotted against time from the beginning of stimulation. Open circles (dashed curves), same for late response (latency 8 msec.). All amplitude values in per cent of the maximal monosynaptic response obtained by stimulation of Point *1* (*p 1*).

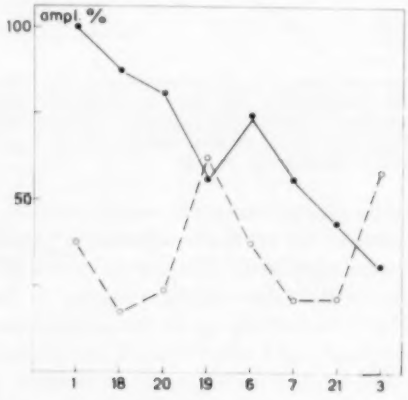


Fig. 9.—Maximal amplitude values of monosynaptic responses (filled circles) and late responses (open circles) in the triceps nerve to contralateral repetitive stimulation of different cortical points (indicated on horizontal axis; cf. map in Fig. 7). Amplitude values in per cent of maximal value obtained (at Point *18*).

20 appeared within one second after the beginning of the repetitive stimulation. These points are included within the circle drawn in full on the map in Figure *7* (the one-second latency field). The field surrounded by a dashed line includes the points the stimulation of which elicited a monosynaptic triceps nerve response within three seconds after the beginning of the repetitive stimulation (the three-second latency field). The dotted circle includes the points from which monosynaptic responses were elicited within seven seconds after the beginning of the repetitive stimulation. When the surrounding cortical areas were stimulated, the monosynaptic response appeared still later during the course of stimulation (e. g., Point *5*; cf. Fig. 8). Thus, judging from the rapidity with which the response is built up by repetitive cortical stimulation, the most effective field for elicitation of the monosynaptic response in the triceps nerve is marked by the inner circle drawn in full.

In the diagram in Figure 9, the maximal amplitude values of the monosynaptic response during the first phase following stimulation of the different points within the whole three-second latency field are plotted in per cent of the highest value obtained. As seen, stimulation of Point *1* gave the highest monosynaptic response. The different points are marked on the horizontal axis. The graph shows that the largest monosynaptic responses were elicited from the area the stimulation of which was also followed by a rapid building up of the monosynaptic response.

Up to this point only the early response following upon each stimulus during repetitive stimulation has been discussed, i. e., the response which, according to our earlier investigations,§ is of monosynaptic order. As was mentioned in connection with the description of Figures 1, 2, 3, and 4, there is also one or several late responses. The late responses are often built up earlier than the monosynaptic response during the course of the repetitive stimulation, this being the case in the experiment illustrated in Figure 1 (record *A*). In other experiments, the late responses are built up in parallel to (Figs. 3 and 4), or more slowly (Fig. 8, Point *1*) than, the monosynaptic response. In the hind leg nerves, the late responses are well marked and are always built up before the appearance of the monosynaptic response.[3] As was the case with the monosynaptic response, the amplitude of the late responses also fluctuates during the course of the repetitive stimulation, and these fluctuations may also show one or two phases. In Figure 9 the amplitude values of one of the late responses, having a latency of about 7 msec., were also plotted (dotted curve). The graph shows that there was no regular arrangement of the points from which the late response could be evoked when the amplitude of the response was considered. It was also found that the late responses could be elicited from a wider area than the monosynaptic response. A comparison of the characteristics of the monosynaptic response and those of the late responses thus shows that the cortical representation of the direct corticomotoneuronal system for one muscle is more restricted than that of the system which is responsible for the late responses.

2. Cortical Representation of the CM System for the Biceps Nerve.—The same types of experiments as those described were performed when leading off the action potentials from the nerve to the biceps muscle. When the contralateral cortical field had been found from which the monosynaptic response in the biceps nerve was most easily elicited, the frequency characteristics of the monosynaptic response

§ References 2 through 4.

were studied, and they were found to be the same as those of the triceps nerve response (Fig. 6). In the biceps nerve also, monosynaptic responses could not be obtained to single cortical stimulation. The records in Figure 10 show the biceps nerve responses to cortical stimulation at varying intervals from the beginning of the repetitive stimulation (frequency of 25 per second). As with the triceps nerve, a monosynaptic response (Fig. 10 *B* to *F*) and a series of late responses were led off from the biceps nerve. Figure 10 shows the phasic behavior of the monosynaptic biceps response. The amplitude of the responses increases to a maximum during the first three seconds (Fig. 10 *A* to *C*) and then decreases. This first phase was followed by a second amplitude rise (Fig. 10 *E* and *F*) within the first 20 seconds after the beginning of the repetitive stimulation if the most potent points and stimulation frequencies (20 to 25 per second) were used.

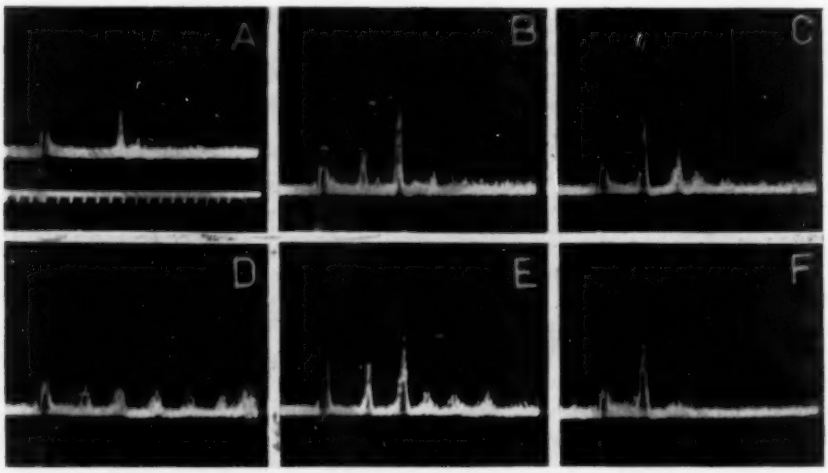


Fig. 10.—Superimposed action potentials in the left biceps nerve following each stimulus in a train of shocks (stimulation frequency 25 per second) delivered to the forelimb subdivision of the right precentral area. The records (*A* to *F*) were taken 1, 2, 3, 8, 9, and 10 seconds, respectively, after the beginning of the repetitive stimulation. Time in milliseconds.

Experiments were then performed in which the cortical representation of the CM system for the biceps muscle was mapped, using the same experimental procedure as in the triceps experiments. The results from such an experiment are plotted in Figure 11 (lower circles), in which the representation of the CM system for the triceps nerve is also marked (upper circles). As seen, there is a restricted field in which stimulation was followed by a monosynaptic biceps response, built up within one second after the beginning of the repetitive stimulation (the one-second latency field; circle drawn in full). The two surrounding circles mark the two- and three-second latency fields.

3. *Reciprocity Between the Monosynaptic Triceps and Biceps Responses.*—It is interesting to note that the circles in Figure 7, representing the different delays in the appearance of the monosynaptic triceps nerve response after the beginning of the repetitive stimulation, have an eccentric orientation. Below the most potent area (the one-second latency field; circle drawn in full) the borders of the two surround-

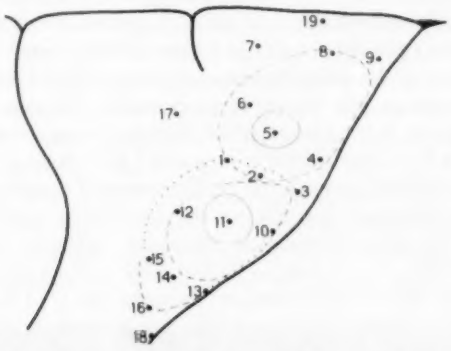


Fig. 11.—Map of the precentral area and orientation of the different points (*1* to *19*) stimulated in the experiments described in the text, in which monosynaptic responses were recorded from the contralateral triceps and biceps nerves (stimulation frequency 25 per second). Upper set of circles indicates the triceps fields (circle drawn in full, one-second latency field; dashed circle, three-second latency field). Lower set of circles indicates the biceps fields (circle drawn in full, one-second latency field; dashed circle, two-second latency field, and dotted circle, three-second latency field). For further explanation, see text.

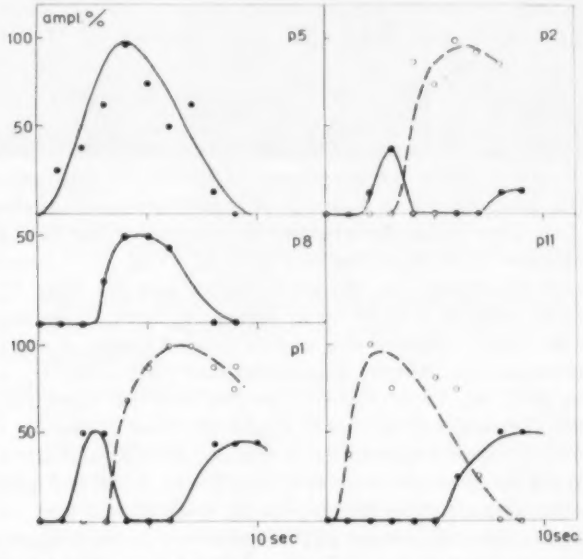


Fig. 12.—Amplitude values of the monosynaptic responses in the nerves of triceps (filled circles, curves drawn in full) and biceps (open circles, dashed curves) to contralateral repetitive cortical stimulation at different points (*5*, *8*, *1*, *2*, and *11*; cf. map in Fig. 11) plotted against time from the beginning of the repetitive stimulation (frequency 25 per second). Amplitude values plotted in per cent of maximal response.

ing fields lie close to each other, whereas above this area the three- and seven-second latency fields are more spread out. Figure 11 shows the results from an experiment in which the cortical representation of the CM system was mapped both for the triceps (upper circles) and for the biceps (lower circles) nerve. As seen, the same eccentric arrangement of the different latency fields was found for the cortical representation of the monosynaptic biceps nerve response. In this case, however, the borders of the different fields (lower set of circles) are closer to each other above the most active area (i. e., toward the triceps area) than below. Thus, if the stimulating electrode was moved upward, out of the restricted area from which high and short latency biceps responses were elicited, the delay in the appearance of the biceps responses during repetitive stimulation increased suddenly when the electrode entered the triceps field. There was no such sudden increase in the delay when the stimulating electrode was moved downward from the center of the biceps field. The sudden delay in the building up of the biceps nerve response thus seems to occur when the field representing the CM system of the antagonist muscle is stimulated.

The behavior of the monosynaptic responses in the nerves to these two antagonistic muscles is further illustrated in Figure 12 (cf. the corresponding map in Fig. 11). The diagrams in Figure 12 are plotted in the same way as those in Figure 8. They show the amplitude fluctuations of the monosynaptic biceps and triceps nerve responses during the repetitive stimulation (25 per second) of different points within the contralateral cortical foreleg subdivision. As shown by the curve drawn in full in Figure 12, stimulation of Point *5* was followed by a rapid building up of the monosynaptic triceps response, which disappeared eight seconds after the beginning of the stimulation period. Actually, Point *5* was the most potent for the triceps response, and no monosynaptic biceps response could be elicited from this point. If the electrode was moved upward to Point *8*, there was still a pronounced monosynaptic triceps response and no biceps response. As expected from the results of the experiments described above, the appearance of the triceps response was slightly delayed. In this connection, it is, however, of importance that the triceps response disappeared, first, after seven seconds, and in this respect the first phase of the amplitude fluctuation is similar to that in Figure 12, Point *5*. If, instead, the electrode was moved downward, i. e., toward the biceps area (to Point *1*), the monosynaptic responses behaved as is shown in Figure 12, Point *1*. As anticipated, the appearance of the triceps response was slightly delayed (curve drawn in full), but in this case the response had already disappeared after three seconds; i. e., the duration of the first phase was more than 50% shorter than that when Points *5* and *8* were stimulated. The same was the case in Figure 12, Point 2, showing the behavior of the monosynaptic triceps response (curve drawn in full) to stimulation at Point *2*, which is also at the border of the biceps field. The dotted curves in Figure 12, Points *1* and *2*, show the behavior of the biceps response when elicited from the same two points. A comparison of the triceps and biceps curves in the diagrams (Fig. 12, Points *1* and *2*) reveals that the depression of the monosynaptic triceps response occurred when the monosynaptic biceps response began to rise. Three seconds after the beginning of the repetitive stimulation monosynaptic triceps responses were recorded, and at that moment there was no monosynaptic biceps response. One second later the biceps response appeared, and at that moment the triceps response disappeared. When the stimulating electrode was then moved to Point *11*, which was the most potent point for the monosynaptic biceps response, this response rose

to a high amplitude within the first second of the repetitive stimulation (Fig. 12, Point *11*), the consequence being that the appearance of the monosynaptic triceps response was delayed six seconds (curve drawn in full). It should also be pointed out that when the monosynaptic triceps responses appeared early from stimulation of Points *1* and *2*, the appearance of the monosynaptic biceps responses was delayed. As soon as the stimulating electrode was moved farther into the biceps area to Point *11*, the delay in the appearance of the biceps response was shortened, there being no early triceps response.

The conclusion to be drawn from these experiments is that there is a reciprocal behavior of the monosynaptic responses in the nerves to the two antagonistic muscles. Stimulation of the lower part of the triceps field counteracts the monosynaptic biceps response elicited from the upper part of the biceps field, and vice versa.

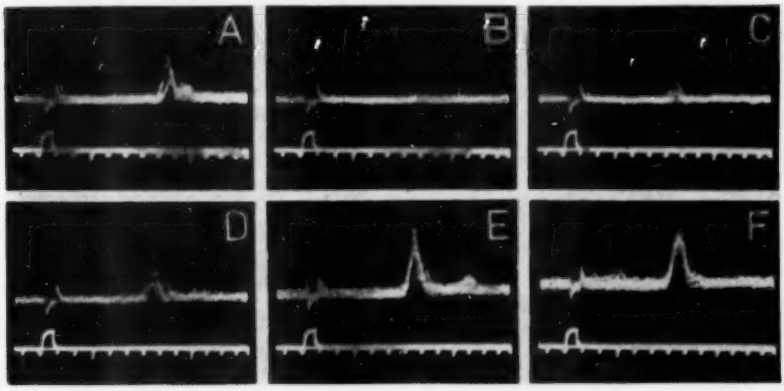


Fig. 13.—Superimposed action potentials in the left thenar nerve following each stimulus in a train of shocks (stimulation frequency 25 per second) delivered to the forelimb subdivision of the right precentral area, (*A*) at the beginning of the stimulation and (*B*) 2, (*C*) 3, (*D*) 4, (*E*) 5, and (*F*) 10 seconds after the beginning of the repetitive stimulation. Time in milliseconds.

Since the preparations were curarized, there were no muscle contractions. Thus the reciprocal behavior of the responses described was not due to afferent back responses from the muscles.

4. *Cortical Representation of the CM System for the Nerves to the Thenar and Hypothenar Muscles.*—Experiments similar to those described above were performed in which the responses to contralateral cortical stimulation were led off from the thenar and hypothenar nerves. Each portion (*A* to *F*) of Figure 13 shows a series of superimposed records of the action potentials following each cortical stimulus in a series of shocks (frequency of 25 per second) applied to the cortical region which was found to be most potent for the elicitation of the thenar nerve responses. This Figure shows the most typical type of response. Immediately at the start of the repetitive stimulation a response appears (Fig. 13 *A*) which disappears during the first seconds (Fig. 13 *B*). After that a response with somewhat shorter latency appears which increases during the fourth and fifth seconds of the repetitive stimulation (Fig. 13*D* to *E*) and then decreases (Fig. 13*F*). The graph in Figure 14 shows the amplitude fluctuations of the deflections during the first 10 seconds of

repetitive stimulation. Actually, the amplitude values of the first-appearing late response (open circles) and those of the early response (filled circles) which appears later during the stimulation period are from eight successive stimulation experiments that were performed during one hour on the same animal with seven-minute intervals. The diagram in Figure 14 shows that the amplitude values of the responses were quite constant during one hour, when this effect was tested.

There are two striking differences which should be noted between the responses obtained from the thenar nerve and those recorded from the triceps and biceps nerves. First, the records of the thenar nerve responses were always characterized by a poverty in late discharges (Fig. 13*C* to *F* and Fig. 21). As described above, the biceps and triceps responses to each single stimulus consist of a whole set of action potentials following upon the monosynaptic response. Second, the cortical stimuli are followed by thenar nerve responses at the very beginning of the repetitive stimulation. Therefore, it was to be expected that single cortical shocks would give thenar nerve responses. As seen in Figure 15 *E*, this was the case. The last-mentioned observation is in agreement with that of Liddell and Phillips [28] who found that single cortical stimuli may evoke movements of the thumb in monkeys. As mentioned above, single cortical stimuli of short duration were never followed by biceps or triceps nerve responses.

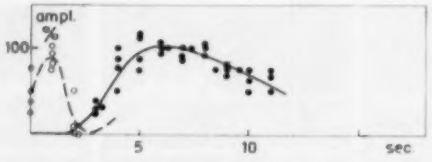


Fig. 14.—Amplitude values of the early (filled circles) and late (open circles) responses in the thenar nerve to contralateral repetitive cortical stimulation with a frequency of 25 per second plotted against time from the beginning of the repetitive stimulation. Amplitude values in per cent of maximal early response.

The first question to be answered was whether the early response in the thenar nerve which appeared during repetitive stimulation (Fig. 13*C* to *F*; cf. curve drawn in full in Fig. 14) was a monosynaptic response. Figure 15 *A* shows superimposed records of the thenar nerve responses to the individual cortical stimuli in a train of shocks (25 per second) when the early response had reached its maximum. The average value of the latency for the early response was 7.0 msec. The time for peripheral conduction in the fast-conducting motoneurones of the thenar nerve was obtained by leading off the thenar nerve response to stimulation of the motoneurones at the ventral root entry zone in the C7 spinal segment (Fig. 15*B*; 4.9 msec.). The latency of the response led off with a needle electrode inserted in the pyramidal tract at the C7 level contralateral to the cortical stimulation is shown in Figure 15C. The cortical response, within the forelimb subdivision, to antidromic stimulation was then led off with the cortical electrode which had previously been used as the stimulating electrode in the spinal cord being used for stimulation. The positions of the electrodes were not changed. The fact that the latency of the cortical response to the antidromic stimulation (Fig. 15*D*) was found to be the same as that of the response to orthodromic stimulation (Fig. 15*C*) strongly favors the view that the latency of the latter represents the conduction time in the corticospinal fibers with

the highest conduction velocity (for further discussion, see Bernhard and Bohm [4]). When the sum (6.2 msec.) of the values for the peripheral (4.9 msec., in Fig. 15*B*) and for the corticospinal (1.3 msec., in Fig. 15*C*) conduction time was subtracted from the latency of the early thenar nerve response to cortical stimulation (7 msec., in Fig. 15*A*), a value of 0.8 msec. was obtained. Since this value, representing the synaptic delay between the corticospinal neurones and the motoneurones, is of the

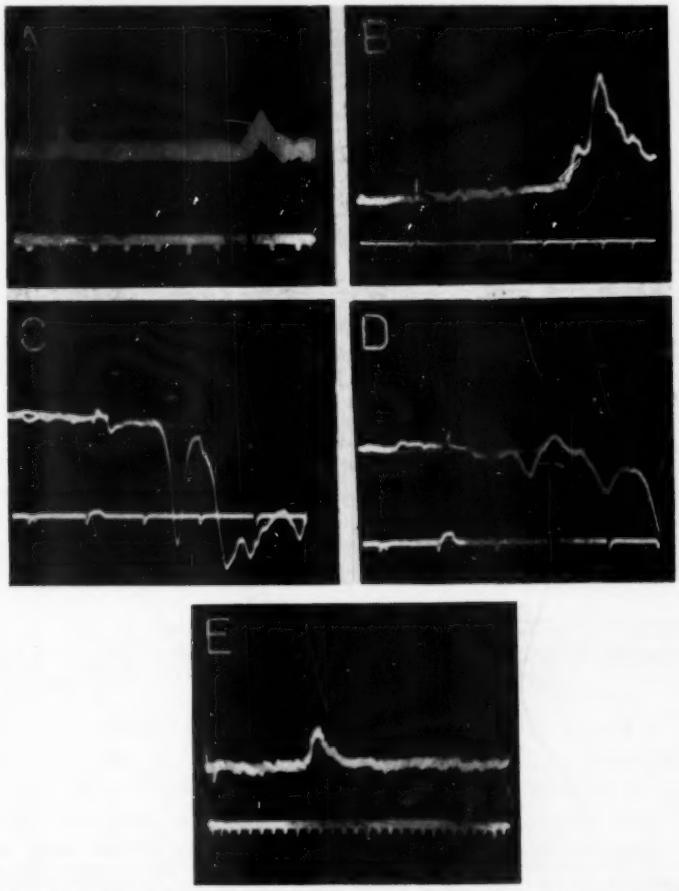


Fig. 15.—*A*, superimposed records of the thenar nerve response to each contralateral cortical stimulation in a train of shocks five seconds after the beginning of repetitive stimulation (frequency 25 per second). *B*, thenar nerve response to stimulation of the motoneurones at the C5 segmental level (dorsal roots cut). *C*, response in lateral pyramidal tract at the C5 level. *D*, antidromic cortical response elicited from the pyramidal tract at the C5 segmental level. *E*, thenar nerve response to a single contralateral cortical stimulation. Time in milliseconds.

same magnitude as that found for monosynaptic transmission elsewhere,‖ we concluded that the thenar nerve motoneurones are also monosynaptically activated by descending volleys in the corticospinal fibers.

‖ References 27, 14, 30, and 25.

The thenar nerve response which appeared at the beginning of the repetitive stimulation, or as a result of single shock stimulation (Fig. 15*E*), had a somewhat longer latency than that of the early response which is built up during the repetitive stimulation.

Different frequencies of repetitive stimulation were tested, and Figure 16 shows the relation between the maximal amplitude to which the monosynaptic response was built up and the stimulation frequency. The curve in Figure 16 shows that the most potent frequencies for the building up of a monosynaptic response were those

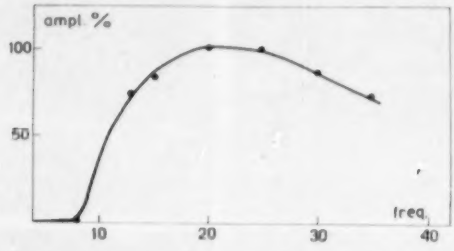


Fig. 16.—Maximal amplitude values of the monosynaptic thenar nerve response to cortical repetitive stimulation at different frequencies plotted against the different stimulation frequencies tested (8 to 35 per second). Amplitude values in per cent of the highest value obtained (at 20 to 25 per second).

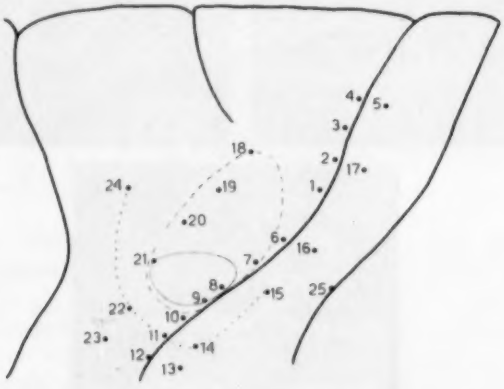


Fig. 17.—Map of the precentral area and orientation of the different points (*1* to *25*) stimulated in the experiment described in the text, in which the monosynaptic responses were recorded from the contralateral thenar nerve (stimulation frequency 25 per second). Circle drawn in full, three-second latency field; dashed circle, five-second latency field, and dotted line, lower border of the eight-second latency field. For full explanation, see text.

of 20 to 25 per second, and therefore these frequencies were used in the following mapping experiments.

The technical procedure in the mapping experiments was the same as that used for the estimation of the cortical representation of the CM system for the biceps and triceps nerves. Figure 17 shows the different points stimulated (*1* to *25*). The solid circle shows the field the stimulation of which was followed by a monosynaptic thenar nerve response, which began to rise within three seconds after the beginning

of the repetitive stimulation; i. e., the delay of the first phase of the amplitude fluctuations was less than three seconds. The dashed circle indicates the five-second latency field, and the dotted line, the lower border of the eight-second latency field. Thus the circle drawn in full marks the most potent field for the elicitation of the monosynaptic thenar nerve response.

The monosynaptic response of the hypothenar nerve was recorded in the same experiments, and Figure 18 shows the results of the mapping of the CM system for the hypothenar nerve. The three different circles indicate the two-, four-, and six-second latency fields. In this preparation, the most potent field for the elicitation of monosynaptic hypothenar nerve responses was situated above that of the thenar nerve (cf. Figs. 17 and 18). In similar experiments we found that these two fields may overlap.

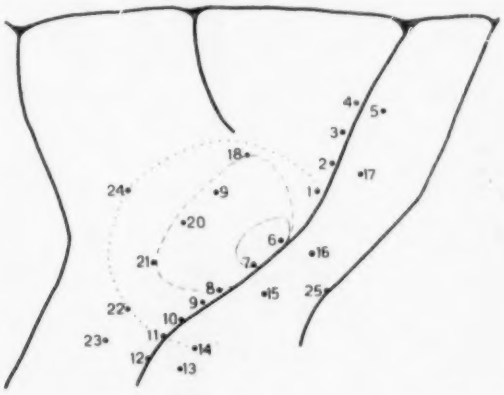


Fig. 18.—Same as in Figure 17 for the monosynaptic hypothenar nerve response. Circle drawn in full, two-second latency field; dashed circle, four-second latency field, and dotted line, anterior border of the six-second latency field.

C. Ipsilateral Cortical Representation of the CM System for Different Nerves

Records were also made of the responses in different nerves ipsilateral to the cortical region stimulated. When the responses were led off from one of the large forelimb nerves, a rather pronounced ipsilateral monosynaptic response was obtained. Figure 19 shows the responses led off from the radial nerves contralateral (upper record) and ipsilateral (lower record) to the cortical forelimb subdivision stimulated. The records were taken three seconds after the beginning of the repetitive stimulation with a frequency of 25 per second, i. e., when the monosynaptic responses had increased to maximal amplitude. The diagrams in Figure 20 show the building up of the ipsilateral and contralateral monosynaptic responses at two different stimulation frequencies (25 and 13 per second). As illustrated in the diagrams, the amplitudes of the ipsilateral and contralateral monosynaptic responses varied in parallel during the repetitive stimulation. It was also found that frequencies between 20 and 25 per second were most potent for the elicitation of the ipsilateral monosynaptic response.

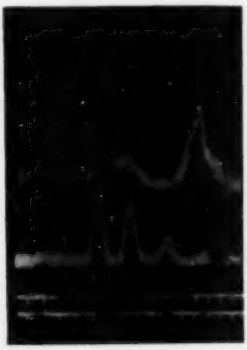


Fig. 19.—Contralateral (upper record) and ipsilateral (lower record) responses in N. radialis to repetitive cortical stimulation (frequency 25 per second). Time in milliseconds. See text.

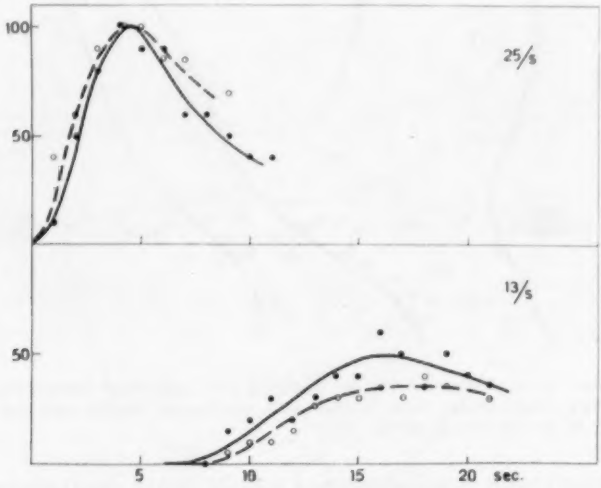


Fig. 20.—Amplitude values of the contralateral (filled circles, curve drawn in full) and ipsilateral (open circles, dashed curve) monosynaptic responses in the radial nerve to repetitive cortical stimulation, plotted against time from the beginning of the repetitive stimulation (25 per second, upper record; 13 per second, lower record).

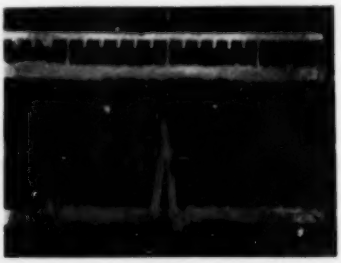


Fig. 21.—Superimposed records of the action potentials in the left (upper records) and right (lower records) thenar nerve following cortical stimulation on the left side. Time in milliseconds.

We also compared the ipsilateral and contralateral responses in the biceps, triceps, thenar, and hypothenar nerves. The monosynaptic responses in the ipsilateral biceps and triceps nerves were similar to those on the side contralateral to the stimulation. It is interesting to note that while monosynaptic responses were regularly obtained from the contralateral thenar nerve, there was no monosynaptic response in this nerve on the ipsilateral side (Fig. 21).

D. Factors Involved in the Building Up of the Monosynaptic Response Elicited by Cortical Stimulation

It was found that each single cortical shock, irrespective of the stimulation frequency, evokes a descending volley in the fast-conducting corticospinal neurones (Fig. 15*C*). This volley fails to cause a monosynaptic discharge in the spinal motoneurones at low stimulation frequencies. When a train of descending volleys is set up by repetitive stimulation, the first volleys are not followed by any mono-

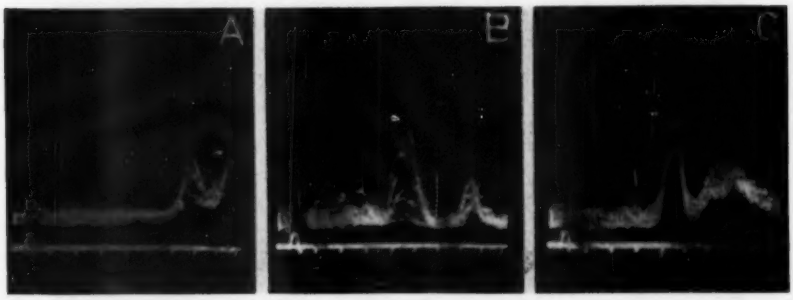


Fig. 22.—Superimposed records of the action potentials in the left radial nerve following each stimulation in a train of contralateral cortical shocks (frequency 25 per second): (*A*) one, (*B*) two, and (*C*) four seconds after the beginning of stimulation. Time in milliseconds.

synaptic motoneurone response. However, during the repetitive stimulation the motoneurones begin to give a monosynaptic response to each single corticospinal volley.

Actually, Figure 1 shows that an irregular continuous discharge appears some seconds after the beginning of the repetitive cortical stimulation. The parallel appearance of the continuous motoneurone discharge and the building up of a monosynaptic motoneurone response is better illustrated in Figure 22. The forelimb subdivision was stimulated with a frequency of 25 per second and the response to the cortical stimulation was recorded from the radial nerve. One second after the beginning of the repetitive stimulation (Fig. 22*A*), there were no irregular continuous discharges on the base line, and the cortical stimuli evoked only long latency responses. In Figure 22*B*, taken two seconds after the beginning of the repetitive stimulation, pronounced continuous discharges can be seen and the monosynaptic response has now appeared. The irregular discharges continued during the next seconds, and there was also a monosynaptic response (Fig. 22*C*). It was found that the asynchronous discharge was built up during the first seconds of stimulation and that it continued after the cessation of the stimulation. Experiments of this type show only that the cortical stimulation elicits a continuous activity in

descending pathways, throwing the spinal motoneurones into an asynchronous activity, which may serve as a facilitatory background to the monosynaptic activation.

Experiments of the type illustrated in Figures 23 and 24 give a more clear-cut demonstration of the building up of a slowly rising facilitatory effect. The monosynaptic reflex in the lumbar region was tested during the period immediately following a burst of repetitive cortical stimulation (25 per second). Figure 23 shows the unconditioned monosynaptic reflex in the L7 ventral root following stimulation of the L7 dorsal root. The conditioning effect on the monosynaptic reflex of a repetitive cortical stimulation was then tested. The conditioning stimulation consisted of a train of shocks (frequency, 25 per second) applied to that part of the contralateral hind limb subdivision which was found to be most potent for the elicitation of a monosynaptic L7 ventral root response. Figure 23*B* shows the monosynaptic reflex spike, tested immediately after the cessation of a cortical stim-

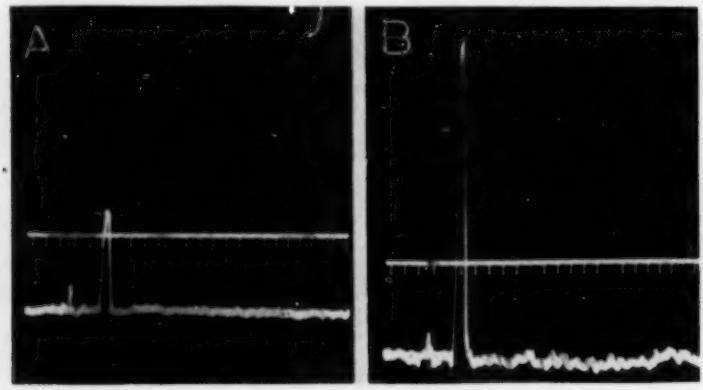


Fig. 23.—Monosynaptic L7 ventral root reflex elicited by stimulation of low threshold fibers in the L7 dorsal root (*A*) before conditioning cortical stimulation, and (*B*) immediately after repetitive cortical stimulation (frequency 25 per second) during three seconds. Time in milliseconds.

ulation lasting three seconds. As seen, the cortical stimulation was followed by a facilitation of the monosynaptic reflex to nearly 400%. The monosynaptic reflex response was then tested after varying periods of cortical stimulation. In Figure 24, the amplitude values of the monosynaptic reflex, tested immediately after cortical stimulation, are plotted against the durations of the preceding conditioning repetitive cortical stimulation. It was necessary to extend the cortical stimulation period to at least two seconds in order to obtain the facilitatory effects. In the same experiment it was found that the building up of the monosynaptic L7 ventral root response to cortical stimulation took two to three seconds. When different frequencies of the cortical stimulation were used, it was found that the building up of the facilitatory action varied in parallel with the building up of the monosynaptic response to cortical stimulation.

Thus, one has to take into consideration (1) that the cortical stimulation, on the one hand, activates the direct corticomotoneuronal system and, on the other hand, elicits a continuous, slowly rising facilitatory action, and (2) that the build-

ing up of the monosynaptic reflex is dependent on the slowly rising facilitation. The facilitatory effect may be transmitted to the spinal level via a system other than the CM system.

It was therefore important to determine that the restricted cortical representation demonstrated in the mapping experiments actually concerned the CM system.

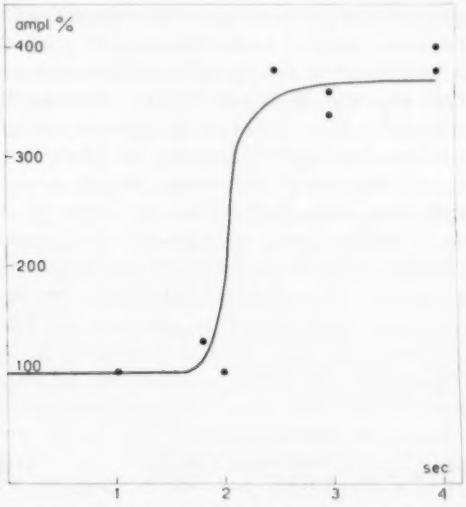


Fig. 24.—Amplitude values of monosynaptic L7 ventral root reflex in per cent of unconditioned value (100%) plotted against duration of preceding conditioning repetitive (25 per second) stimulation of contralateral cortical hind limb subdivision.

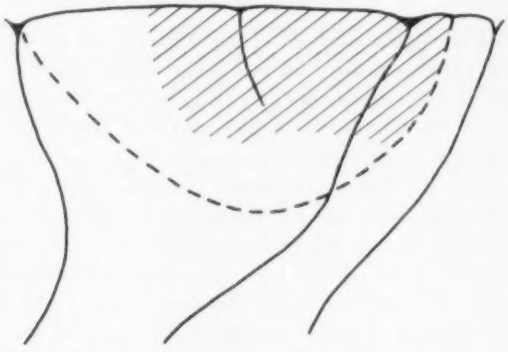


Fig. 25.—Map of precentral area. Shaded area above shows the field from which monosynaptic L7 ventral root response to repetitive cortical stimulation was elicited (duration of stimulation four seconds). Field surrounded by dashed line shows the cortical field from which facilitation of the monosynaptic L7 ventral root reflex was obtained.

Experiments performed for other reasons by Bernhard and Bohm [4] actually showed this to be the case. In those experiments a recording needle electrode was inserted into the pyramidal tract at the L1 level. At this level the pyramidal tract comprises

only fibers for the hind leg and tail. Twenty different points on the contralateral cortex were then stimulated, one after another. It was found that the cortical representation for the pyramidal responses in the L1 segment comprised only the hind leg subdivision. Thus, there is a restricted cortical representation of those corticomotoneuronal fibers which give rise to the monosynaptic response.

The question of the spatial relation between the cortical representation of the facilitatory effect on a certain group of spinal motoneurones and that of the CM system activating the same group of motoneurones is of great interest in this connection. To obtain an answer to this question, experiments were carried out of the same type as that illustrated in Figure 24, the difference being that the conditioning cortical stimulation was applied to 20 different cortical points in succession. A train of repetitive shocks, with a frequency of 25 per second and a duration of four seconds was used for cortical stimulation, and the responses were recorded from the L7 ventral root. The shaded area in Figure 25 shows the cortical field the stimulation of which elicited contralateral monosynaptic L7 ventral root responses. The facilitation of the monosynaptic L7 ventral root reflex was estimated after each stimulation period. The whole field surrounded by the dashed line shows the cortical field from which facilitation of the monosynaptic L7 ventral root reflex could be elicited. The interesting point, in this connection, is that the cortical area the stimulation of which had a facilitating action on the L7 monosynaptic reflex is much more widespread than the field the stimulation of which elicited a monosynaptic L7 ventral root response, the characteristics of the cortical stimulation being the same in the two cases. These experiments thus show that a certain group of motoneurones, which are monosynaptically activated by descending volleys in the CM system, is facilitated by stimulation of a field which does not merely cover, but actually exceeds, the restricted field the stimulation of which activates the CM fibers to this group of motoneurones.

COMMENT

In the electrophysiological analysis of the organization of different functional units in the central nervous system, the estimation of the delays in the relay nuclei which are engaged in the transmission plays a great role, since such measurements give an indication of the complexity of the functional system studied.

With regard to the spinal reflexes, Ramón y Cajal,[9] on histological grounds, differentiated between the reflex arcs which comprise interneurones intercalated between the afferent collaterals and the motoneurones and those arcs in which the afferent fibers articulate directly with the motoneurones. Electrophysiological evidence for the existence of the second type, the so-called monosynaptic arc, in cats was given by Eccles and Pritchard [14] and Renshaw,[30] who found the central delay of the ventral root response to dorsal root stimulation to be of the same magnitude as the delay for synaptic activation of the oculomotor neurones by a presynaptic volley, shown by Lorente de Nó.[27] The functional significance of the monosynaptic spinal reflexes for myotatic activity in cats was shown by Lloyd.[26] Electrophysiological evidence for direct activation of the motoneurones from the afferent neurones in monkeys has also been found.[3]

In the corticospinal system in cats, Szentágothai-Schimert,[34] on the basis of degeneration experiments, stressed that the pyramidal neurones end within the

regions of the internuncial nuclei, and not at the motoneurones. These histological findings are in agreement with the results of the electrophysiological investigations on cats made in the same year by Lloyd,[24] who concluded that cells in the external basilar region, as well as those in the intermediate gray nucleus, constitute relays between the pyramidal fibers and the motoneurones. His experiments were performed on the lumbar region, and from our investigations on cats [6] the corticospinal activation of motoneurones in the cervical region is also of polysynaptic order in this animal.

In monkeys (Macacus mulattus), on the other hand, Hoff and Hoff [19] found that extirpation of Area 4 was followed by degeneration of terminals, not only in the intermediate zone of the gray matter but also in the vicinity of the spinal motoneurones. Not until recently has electrophysiological evidence been presented for direct monosynaptic activation of spinal motoneurones by descending volleys in the corticospinal fibers.¶ The fraction of the corticospinal fibers which activates the motoneurones directly we have chosen to call the CM system. Evidence is presented by Bernhard and Bohm [5] that the CM fibers traverse the pyramids and that those corticospinal fibers which have the highest conduction velocity belong to the CM system.¶ Thus, there is not only the difference between the cat and monkey in the number of the fibers in the so-called pyramidal tract [2] but also the difference that in the pyramidal tract of the monkey a CM system has developed which does not exist in the cat.

When we found functional evidence for the existence of a CM system in the monkey, we thought that there might be a relationship between the existence of the CM system and the special pattern of the muscular activity which monkeys, primates, and humans develop when moving their hands and fingers. The difference in the movement pattern between an animal with paws, e. g., the cat, and an animal with hands, e. g., the monkey, concerns not only the activity of the muscles serving the digits but, more or less, that of all the muscles of the extremities. A monosynaptic system would be more apt to serve movement patterns in which there is a great demand on the regulation of the activity in restricted muscles or muscle groups, as is the case in an extremity equipped with a hand, since in such a system there are a priori fewer possibilities of functional divergence than in a polysynaptic system. Bernhard, Bohm, Petersén, and Taverner [6] performed mapping experiments on the cat, of the same type as those described above, in which the cortical representation was estimated for the responses in different foreleg nerves, these responses being of polysynaptic order. No spatial separation could be found of the cortical fields from which the low-threshold responses in different foreleg nerves could be elicited. Thus, the cat experiments showed that the most potent fields for the elicitation of responses in, e. g., Nn. triceps, biceps, ulnaris, and medianus had a wide extension and overlapped almost entirely.

Numerous investigations in which the movements of different parts of the extremities or the contractions of different muscles were recorded have shown that in the monkey (e. g., Macacus mulattus) there is a specialized pattern of cortical representation. The present results show that the corticospinal neurones

¶ References 2 through 4.

which, according to these and earlier investigations,# activate the spinal motoneurones monosynaptically, i. e., the CM fibers, have such a specialized pattern of cortical representation. While in the cat a descending volley set up by stimulation at a cortical point is bound to evoke widespread muscular activity, owing to the divergence in polysynaptic relay systems, stimulation at one cortical point in the monkey activates a group of CM fibers the descending volleys in which activate a much more restricted group of motoneurones by direct action. This difference between the cat and the monkey in the organization of the spinal integration mechanism of the corticospinal system seems to us to be of great importance.

The conclusions to be drawn regarding the cortical representation must be examined carefully in the light of the experimental procedure used. In the investigations made by previous authors on the analysis of the corticospinal system in monkeys, the movements or muscle contractions resulting from cortical stimulation were recorded. In our experiments, the responses were recorded in different peripheral nerves to single cortical stimuli, as well as to each stimulus in a train of cortical shocks. A single cortical shock elicits a descending volley in the fast-conducting corticospinal neurones of the pyramidal tract (Fig. 15). The experiments presented above show that single cortical shocks do not elicit any monosynaptic responses in the different forelimb nerves tested. Repetitive stimulation had to be used, and during the course of stimulation the monosynaptic responses were built up in a regular way. It was shown that the repetitive cortical stimulation builds up a long-lasting facilitatory action, which successively raises the excitability of the motoneurones, and, further, that when the facilitatory action reaches a certain level, the monosynaptic responses to the descending volleys in the fast-conducting CM fibers break through. It was also found that the cortical field from which the facilitation of a certain group of spinal motoneurones was elicited not only covered the restricted cortical field representing the CM system which activates the same group of motoneurones, but also exceeded it (Fig. 25). It is of great interest to note that "the facilitatory area" and "the CM area" for the same group of spinal motoneurones have the same posterior border toward the postcentral gyrus, whereas the "facilitatory area" extends in the anterior direction.

It was also found that an asynchronous continuous discharge appears in the motoneurones in parallel to the building up of the facilitatory activity during the repetitive cortical stimulation, and that this "tonic" activity outlasts the cortical stimulation, as does the facilitatory action. The "poststimulatory" continuous motoneurone activity which builds up during stimulation seems to be equivalent to the "tonic after-discharge" described by Graham-Brown and Sherrington.[16] The results of an investigation on the correlation of the facilitation, the tonic after-discharge, the activation of the monosynaptic response to cortical stimulation, and the electrical cortical activity will be published.[7]

The recording from different nerves of the activity of the action potentials which follow upon each stimulus in a train of cortical shocks reveals that the monosynaptic response to each individual shock is followed by a series of

References 2 through 4.

responses with longer latencies. Less attention has been paid to these late responses in this investigation, but it should be pointed out that the cortical field the stimulation of which evoked the late responses in a certain nerve had a wider extension than the field from which the monosynaptic responses were elicited. The diagram in Figure 9 shows, in addition, that there is not the same strict cortical topography of the cortical field from which the late responses could be elicited. It is probable that the late responses are mediated over internuncial relay systems at suprasegmental or segmental levels, or both. An important point is the poverty of the late responses in the nerves to distal muscles in the extremities (e. g., thenar and hypothenar muscles in the hand) as compared with the massive late responses which usually appear in the nerves to the proximal muscles of the arm (biceps and triceps).

Thus, from the results presented above, it may be concluded that in the monkey weak repetitive stimulation during a short period (e. g., 3 to 5 seconds with stimulation frequency of 25 per second) gives rise to the following events: (1) monosynaptic responses to the individual shocks in a relatively restricted group of motoneurones; (2) late responses (probably polysynaptic) in the same and other motoneurones with a wider peripheral distribution; (3) a facilitatory action on the same and additional motoneurones; (4) a "tonic" asynchronous discharge in these and additional motoneurones, and, finally, (5) concomitant inhibitory action due to stimulation of adjacent points, the stimulation of which is followed by a reciprocal effect, as shown in Figure 12.

Great care is needed when drawing conclusions about cortical organization on the basis of experiments in which the muscle contractions or movements are recorded, since these may represent the sum of these different activities, which may partly be the result of activity in different descending systems. These factors may explain why different investigations based on the recording of muscle contractions and movements have led to different conclusions as to the cortical representation of, e. g., the so-called pyramidal system.

From the present investigation, it is clear that the cortical representation for the monosynaptic response in a certain nerve is more restricted than the fields from which the other activities in the motoneurones of the same nerve could be evoked. Great attention was paid to the topography of the cortical fields from which the monosynaptic responses in the nerves to two antagonistic forelimb muscles could be evoked. They all (five different preparations) showed that the cortical fields for the representation of the CM system of the biceps and triceps nerves were spatially separated. According to Boynton and Hines,[8] a single muscle may contract to weak repetitive cortical stimulation, and on the basis of experiments on monkeys in which the contractions of several muscles in the foreleg were polygraphically recorded, Chang, Ruch, and Ward[10] concluded that the "solitary response points" for a given muscle are not scattered at random but fall into groups. It is highly probable that in these experiments the monosynaptically transmitted activity was the dominant factor for the muscle responses recorded. In a classic investigation, Sherrington and Hering[33] described excitation and inhibition of limb antagonists to cortical stimulation. The effect may, however, be due to, or partly due to, afferent back responses from the muscles

during the contraction. Actually, such a peripheral influence had been excluded in the ingenious experiments by Sherrington [32] on the cortical activation of the eye muscles. Our experiments show that in the case of spinal motoneurones also a reciprocal excitation and inhibition of the monosynaptic responses in the nerves to antagonists can be elicited by cortical stimulation in the absence of influence from the muscle receptors, since in our experiments the preparations were curarized. The importance of excluding the proprioceptive inflow when attacking this problem is obvious from the interesting results which were recently published by Gellhorn and Hyde.[15]

All earlier investigations on the representation of the musculature in the so-called motor areas, based on the recording of movements or muscle contractions, agree that the distal segments of a limb have a more extensive cortical representation than the proximal segments. This rule holds true for monkeys,[35] anthropoid apes,[22] and humans.* Our experiments indicate that this rule may apply to the CM system, the thenar and hypothenar fields for monosynaptic response being slightly larger than the biceps and triceps fields.

It is difficult at this stage to draw any far-reaching conclusions as to the participation of monosynaptic activity in the muscle contractions and movements elicited by cortical stimulation in primates and man. The following considerations based on the present knowledge are, however, of interest in this connection. It is a well-known fact that the variety and individuality of movements elicitable by cortical stimulation are greater for the distal than for the proximal musculature (see, e. g., review by Ruch [31]). As mentioned above, a monosynaptic activation system would be more apt to serve such a mechanism than a polysynaptic one. Since during repetitive cortical stimulation monosynaptic responses in the nerves to the distal hand muscles developed which were followed by relatively poor late discharges, it seems that the CM system actually plays the dominant role for the cortically evoked contractions in the distal hand muscles when repetitive stimulation is used. Further, our experiments indicate that in the Macacus monkey the CM system for the distal hand muscles has a contralateral representation only. In view of the results of Penfield and Rasmussen [29] showing that in man only contralateral responses in the limbs could be obtained by cortical stimulation, the assumption could be made that a CM system with contralateral cortical representation plays a still more important role in man than in the monkey for the corticospinal activation of both distal and proximal muscles in the extremities.

We are well aware of the difficulty of drawing conclusions as to the importance of the CM system for the performance of voluntary movements, recalling the pertinent sentence in Penfield and Rasmussen's book [29]: "It is a far cry from the gross movements produced by cortical stimulation to the skilled voluntary movements of the hand of the man and the monkey." With this type of experiment it must also be remembered that "electrical excitation demonstrated an important and localized motor effect rather than a specialized motor act," as expressed by Denny-Brown and Botterell.[13] The last-mentioned authors express the view that after extirpation of Area 4 in the Macacus monkey, even the movements in the hand return after a period of loss, but that they are never again as perfectly integrated. The assumption

* References 28 and 29.

that damage to the CM system plays a role for this moderate motor deficiency in the Macacus monkey fits in with the fact that damage to Area 4 is followed by more serious deficiencies in man, an application of the working hypothesis that a contralaterally represented CM system for the hand muscles is more developed and plays a greater role in humans.

The activity signaled by the long-latency discharges which follow upon the monosynaptic response to each cortical shock, and which could be evoked from more extensive cortical fields than the monosynaptic discharge, is well represented in the nerves to proximal arm and hand muscles. These discharges may play a role in integrated gross movements which are more engaged in posture than the finger movements governed by distal hand muscles. If the assumption is correct that in man, as in monkeys, both the CM system and the descending system giving rise to the long-latency discharges are engaged in the cortically induced activation of the proximal forelimb muscles, whereas for the cortical activation of the distal muscles the CM system is the dominant factor, it follows that the cortically induced finger movements should be more susceptible to local central damage than the cortically induced gross movements in the proximal parts of the forelimb, as is actually the case.

SUMMARY AND CONCLUSIONS

Single and repetitive square-wave shocks of short duration (0.5 to 1 msec.) were used for stimulation of the cortex in narcotized, curarized monkeys, and the action potentials were led off from different peripheral nerves in the forelimb. The effect of cortical stimulation on the monosynaptic ventral root reflex in the lumbar region was also studied.

Attention was chiefly paid to the characteristics and cortical representation of the corticomotoneuronal system (the CM system) earlier described by Bernhard, Bohm, and Petersén † and by Bernhard and Bohm.[4]

The experiments in which recordings were made from different nerves of the action potentials which follow upon each cortical stimulus in a train of shocks, as well as those in which the monosynaptic reflex was tested after conditioning cortical stimuli, show that weak repetitive cortical stimulation gives rise to the following events in the nerves on the contralateral side.

1. Each shock elicits a descending volley in the corticomotoneuronal fibers of the pyramidal tract. This volley does not elicit any monosynaptic response in the spinal motoneurones unless the stimulation frequency is increased above 10 per second.

2. Higher stimulation frequencies (15 to 30 per second) successively build up a long-lasting facilitatory action on the spinal motoneurones.

3. When this facilitatory effect has reached a certain level, a monosynaptic response to each descending volley in the corticomotoneuronal fibers breaks through in the spinal motoneurones.

4. Apart from the monosynaptic response, each cortical shock may be followed by a series of late responses (probably polysynaptic), which are more pronounced in the nerves to the proximal arm muscles than in those to the distal hand muscles.

† References 2 and 3.

5. A "tonic" asynchronous discharge is built up during the course of repetitive stimulation.

6. Finally, inhibitory effects on the monosynaptic motoneurone response are evoked.

Among the different frequencies tested, those between 20 and 25 per second were found to be most convenient for the building up of the facilitatory effect, mentioned in paragraph 2. These frequencies were therefore used in the experiments in which the cortical representation of the CM system for the nerves to different forelimb muscles was mapped.

It was found that the cortical field from which the monosynaptic response in a certain nerve could be elicited was more restricted than those from which the late responses and tonic discharges in the same nerve could be evoked. It was also found that the cortical field from which facilitation of a certain group of motoneurones could be evoked had a greater extension in the anterior direction than the cortical field from which a monosynaptic response in the same group of motoneurones could be elicited. Since among the cortical fields from which the different activities in a certain group of motoneurones could be elicited, that for the monosynaptic response was most limited, it is concluded that among the different corticospinal systems the direct corticomotoneuronal one (the CM system) has the most restricted cortical representation.

It was found that the cortical representations of the CM system activating the nerves to the biceps and triceps muscles were spatially separated. Our experiments also showed that reciprocal excitation and inhibition of the monosynaptic responses in these two nerves to antagonistic muscles could be elicited by cortical stimulation in the absence of peripheral influences.

The cortical representation of the CM system for the nerve to the thenar muscles (adduction of the thumb) seems to be but slightly larger than those of the CM system for different proximal arm muscles.

The experiments show that the CM systems for the nerves to the proximal arm muscles also have an ipsilateral cortical representation, whereas they indicate that this is not the case for the CM systems activating the nerves to the distal hand muscles, in which only contralateral monosynaptic responses to cortical stimulation could be recorded.

On the basis of the results presented, the difference between the spinal organization of the corticospinal system in monkeys and cats is discussed.

Finally, the role of the CM system for the cortically induced movements in monkeys, as well as the possible role of a CM system for the voluntary movements in humans, is discussed.

REFERENCES

1. Adrian, E. D., and Moruzzi, G.: Impulses in Pyramidal Tract, J. Physiol. **97**:153-199, 1939.

2. Bernhard, C. G.; Bohm, E., and Petersén, I.: New Investigations on the Pyramidal System in Macaca Mulatta, Experentia **9**:111-112, 1953.

3. Bernhard, C. G.; Bohm, E., and Petersén, I.: Investigations on the Organisation of the Cortico-Spinal System in Monkeys (Macaca Mulatta), Acta physiol. scandinav. (Supp. 106) **29**:79-105, 1953.

4. Bernhard, C. G., and Bohm, E.: Monosynaptic Corticospinal Activation of Fore Limb Motoneurones in Monkeys (Macaca Mu'atta), Acta physiol. scandinav., to be published.

5. Bernhard, C. G., and Bohm, E.: To be published.

6. Bernhard, C. G.; Bohm, E.; Petersén, I., and Taverner, D.: To be published.

7. Bernhard, C. G.; Bohm, E., and Taverner, D.: To be published.

8. Boynton, E. P., and Hines, M.: On Question of Threshold in Stimulation of Motor Cortex, Am. J. Physiol. **106**:175-182, 1953.

9. Ramón y Cajal, S.: Histologic du système nerveux de l'homme et des vertébrés, Paris, A. Maloine, 1909.

10. Chang, H. T.; Ruch, T. C., and Ward, A. A., Jr.: Topographical Representation of Muscles in Motor Cortex of Monkeys, J. Neurophysiol. **10**:39-56, 1947.

11. Cooper, S., and Denny-Brown, D.: Responses to Rhythmical Stimulation of the Cerebral Cortex, A. Res. Nerv. & Ment. Dis., Proc. (1947) **27**:235-345, 1948.

12. Cooper, S., and Denny-Brown, D.: Responses to Stimulation of the Motor Area of the Cerebral Cortex, Proc. Roy. Soc., London, s. B. **102**:222-236, 1927.

13. Denny-Brown, D., and Botterell, E. H.: Motor Functions of the Agranular Frontal Cortex, A. Res. Nerv. & Ment. Dis., Proc. (1947) **27**:235-345, 1948.

14. Eccles, J. C., and Pritchard, J. J.: Action Potential of Motoneurones, J. Physiol. **89**:43P-45P, 1937.

15. Gellhorn, E., and Hyde, J.: Influence of Proprioception on Map of Cortical Responses, J. Physiol. **122**:371-385, 1953.

16. Graham-Brown, T. G., and Sherrington, C. S.: On the Instability of a Cortical Point, Proc. Roy. Soc., London, s. B. **85**:250-277, 1912.

17. Häggqvist, G.: Faseranalytische Studien über die Pyramidenbahn, Acta psychiat. et neurol. **12**:457-466, 1937.

18. Hoff, E. C.: Central Nerve Terminals in Mammalian Spinal Cord and Their Examination by Experimental Degeneration, Proc. Roy Soc., London, s. B. **111**:175-188, 1932.

19. Hoff, E. C., and Hoff, H. E.: Spinal Terminations of the Projection Fibres from the Motor Cortex of Primates, Brain **57**:454-474, 1934.

20. Lassek, A. M.: Pyramidal Tract: Study of Large Motor Cells of Area 4 and Fiber Components of Pyramid in Spider Monkey (Ateleus Ater), J. Comp. Neurol. **79**:407-413, 1943.

21. Lassek, A. M.: Pyramidal Tract: Basic Considerations of Corticospinal Neurons, A. Res. Nerv. & Ment. Dis., Proc. (1947) **27**:106-128, 1948.

22. Leyton, A. S. F., and Sherrington, C. S.: Observations of the Excitable Cortex of the Chimpanzee, Orangutan, and Gorilla, Quart. J. Exper. Physiol. **11**:135-222, 1917.

23. Liddell, E. G. T., and Phillips, C. G.: Thresholds of Cortical Representation, Brain **73**:125-140, 1950.

24. Lloyd, D. P. C.: Spinal Mechanism of the Pyramidal System in Cats, J. Neurophysiol. **4**:525-546, 1941.

25. Lloyd, D. P. C.: Reflex Action in Relation to Pattern and Peripheral Source of Afferent Stimulation, J. Neurophysiol. **6**:111-119, 1943.

26. Lloyd, D. P. C.: On the Reflex Actions of Muscular Origin, A. Res. Nerv. & Ment. Dis., Proc. (1950) **30**:48-67, 1952.

27. Lorente de Nó, R.: Synaptic Delay of Motoneurones, Am. J. Physiol. **111**:272-282, 1935.

28. Penfield, W., and Boldrey, E.: Somatic Motor and Sensory Representation in Cerebral Cortex of Man as Studied by Electrical Stimulation, Brain **60**:389-443, 1937.

29. Penfield, W., and Rasmussen, T.: The Cerebral Cortex of Man, New York, The MacMillan Company, 1950.

30. Renshaw, B.: Activity in Simplest Spinal Reflex Pathways, J. Neurophysiol. **3**:373-387, 1940.

31. Ruch, T. C., in Stevens, S. S.: Handbook of Experimental Psychology, New York, John Wiley & Sons, Inc., 1951, Chap. 5, p. 154.

32. Sherrington, C. S.: Further Experimental Note on the Correlation of Action of Antagonistic Muscles, Proc. Roy. Soc., London, s. B. **52**:407-320, 1893.

33. Sherrington, C. S., and Hering, H. E.: Antagonistic Muscles and Reciprocal Innervation, Proc. Roy. Soc., London, s. B. **62**:183-187, 1897.

34. Szentágothai-Schimert, J.: Die Bedeutung des Faserkalibers und der Markscheidendicke in Zentralnervensystem, Ztschr. Anat. u. Entwcklungsgesch. **111**:201-223, 1941.

35. Woolsey, C. N.; Settlage, P. H.; Meyer, D. R.; Sencer, W.; Hamuy, T. P., and Travis, A. M.: Patterns of Localization in Precentral and "Supplementary" Motor Areas in Their Relation to the Concept of a Premotor Area, A. Res. Nerv. & Ment. Dis., Proc. (1950) **30**:238-264, 1952.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Richard M. Brickner, M.D., President, New York Neurological Society, Presiding

Joint Meeting, Feb. 9, 1954

Role of Pudendal Nerve in Neurogenic Bladder Disturbances. Dr. Andor A. Weiss (by invitation).

Pudendal nerve blocks and neurectomies have been used in cases of neurogenic bladder in an attempt to restore the balance between the forces of expulsion and retention.

In 1939 Huggins, Walker, and Noonan obtained good results in five of seven tabetics when they combined pudendal neurectomy with presacral neurectomy or transurethral resection. Emmett, Daut, and Dunn, in 1946, failed to restore balance in a traumatic cord bladder. A pudendal nerve section was unsuccessful, after repeated transurethral resections of the bladder neck. Nesbit was successful in one case of traumatic cord bladder in 1948.

A situation analogous to biliary dyskinesia is found in some patients after recovery from spinal shock. The detrusor contractions are not accompanied by relaxation of the sphincters. The patients are unable to void, and there are severe autonomic manifestations. This condition was studied at the Bronx VA Paraplegic Center with electromyography and at the Long Beach Calif., VA Center with cystoscopy before and after pudendal nerve block and neurectomy. With effective nerve block, the marked electrical activity of the pelvic floor subsided entirely and the patient voided with a good stream. In some cases repeated pudendal nerve blocks sufficed to restore balance, but where the results were good, but temporary, bilateral pudendal neurectomies were performed.

Two quadriplegics with bilateral pudendal neurectomy failed to show the good results obtained at the time of pudendal blocks. Bors, in his series of 15 cases, obtained good results in 14 paraplegics and 1 failure in a quadriplegic. Following bilateral pudendal neurectomy the bladder becomes responsive to external pressure. The failure to obtain good results in the quadriplegics may have been due to their inability to apply the Credé maneuver.

DISCUSSION

Dr. Arthur S. Abramson (by invitation): When we started working on the problem of the neurogenic bladder, it was felt that the activity of the striate muscle in the pelvic floor was very important. In electromyography we had a useful tool for observing this activity directly. The insertion of the coaxial needle electrode into the levators is simple. We were particularly interested in the problem of balance (reciprocal action) between the expulsive force and the force of retention. In the spastic bladder, the levators probably reflect the activity of the entire striate musculature of the pelvic floor, including the external sphincter. In the normal, it was noted that the pelvic floor relaxed prior to detrusor contraction. In the spastic, we found that as the bladder filled there was a gradual increase in electric activity in the pelvic floor, even though the cystometric curve did not rise. The increase in activity became marked as soon as the cystometric curve began to rise. The activity persisted as long as the cystometric curve rose and as long as filling of the bladder continued. When the addition of fluid was stopped, there was a tendency for the activity of the pelvic floor to die down. This condition is different than that found in the normal bladder, in which the pelvic floor is electrically silent when the detrusor muscle is contracting. When the pudendal nerve was blocked on one side, the activity on that side was greatly reduced. When the pudendal nerve was blocked bilaterally, there was a great deal less electric activity of the pelvic floor, and sometimes the muscle was completely silent. At this point the patient was asked to void. These studies were done in patients who were previously incapable of voiding and who required continuous catheterization. The patient was able to void, but not in a continuous stream. Voiding had to be reinforced by pressure upon the bladder above the symphysis. We considered this method of voiding an adequate one.

DR. THOMAS I. HOEN: I should like to know whether you have come to any conclusion in regard to the differences in interrupting the pudendal nerve and sectioning the anterior roots of the sacral nerves. In the first instance both sensory and motor components are interrupted; in the latter the sensory component is spared. In other words, is the relaxation of the external sphincter due to the interruption of the anterior motor roots supplying it or to the abolition of the reflex arc? In the work we did, we felt that interruption of the roots was enough to give relaxation of the external sphincter. Some differentiation might be made between anterior root section and interruption of the pudendal nerve.

DR. ARTHUR S. ABRAMSON: We directed our attention to the sensory component of the pudendal nerve, on the basis of our hypothesis. We felt that the effect of its interruption was very similar to the effect which is developed by section of the obturator nerve. If the adductor was denervated, there was an over-all reduction in spasticity, even in muscles which were not denervated. Our interest was in trying to maintain the power of the expulsive force of the detrusor, at the same time trying to reduce the forces of retention. Establishment of such a condition would mean a better-balanced bladder than that obtained by root section. The rhizotomy would mean that a much weaker expulsive force would be produced at the same time that the forces of retention were being reduced.

DR. ANDOR A. WEISS: I think Dr. Abramson has summarized our attitude very well. We are well aware of your work, Dr. Hoen. We did use sacral denervation. We used both anterior and posterior rhizotomy from S2 through S5, but, as Dr. Abramson pointed out, our chief interest was in trying to eliminate the forces of retention without weakening the detrusor. We did sphincterometric readings. In all these cases we got readings much above the normal of 20 to 40 mm. Hg. We have had some experience with sacral rhizotomy in patients who exhibited severe autonomic phenomena. Not only was there clinical relief, but after the sacral rhizotomy we were unable to induce hypertension and other phenomena by distending the bladder or stretching the anal sphincter.

"Postconcussion Syndrome" in Compensation and Litigation: An Analysis of Ninety-Five Cases with EEG Correlations. DR. PETER G. DENKER and DR. GERALD F. PERRY (by invitation).

The histories of 95 cases of "postconcussion syndrome" involved in litigation for compensation were consecutively reviewed. Clinical opinions as to degrees of organic *versus* functional components in these cases were proposed, and a correlation was attempted with the aid of electroencephalography in all these cases.

Definite abnormalities were found in 55% and borderline readings in 3% of this series, despite the absence of positive neurologic findings on examination.

The types of brain wave abnormalities found were listed, the commonest being focal slow waves, although amplitude asymmetries were also of great significance. Fast activity was rarely seen.

Similar changes were found in recent head injuries, of less than three months' duration, as compared with those of older cases, in which the head injury had occurred one to two years previously.

In approximately 80% of the cases the clinical impression was confirmed by the electroencephalographic findings. In the other 20% such a clinical impression was at variance with that of the electroencephalographic findings.

No correlation between loss of consciousness and abnormal electroencephalograhic findings could be determined.

DISCUSSION

DR. SAMUEL BROCK: Drs. Denker and Perry have added another noteworthy paper to a distinguished list in which it has been attempted to analyze the postconcussion syndrome. They cite the well-known fact that from 15 to 30% of persons have persistent headaches, dizziness, and personality changes for a variable period following relatively slight head injury. They point out that litigational and/or compensation factors have helped to make this a puzzling and highly complicated problem. The ideal set-up for studying this problem would be (1) a pretraumatic study of a large group of workers in an industry in which head injury is common—this should include not only the usual neurologic examinations but also a study of the personality

profile and interpersonal relationships, etc., as well as electroencephalography; (2) the establishment of a brain injury center to which such injured persons could be sent so that they could be studied with some degree of uniformity, and (3) of great importance, a follow-up study covering a number of years, the period depending upon the duration of the symptoms.

DR. HANS STRAUSS: In my own similar material, of 250 cases, the incidence of electroencephalographic abnormality is exactly 20%. This incidence is only 10% in patients without disturbances of consciousness. In those with such disturbances the percentage is higher when the unconsciousness lasted more than one hour. Statistics do not help us much in this type of work, except that we should be aware of what really constitutes an abnormal EEG. The difference in these criteria must account for our difference in results.

DR. A. DAVIDSON: On the neurological service with which I am associated we make great use of an ancillary factor, i. e., psychologic tests—the Wechsler Memory Scale, the Bellevue-Wechsler (digit symbol, block design, and similarities) test, and the Bender visual motor gestalt test. In a recent paper in the *American Journal of Psychiatry* in which the EEG and psychologic tests were compared, it was found that psychologic tests were much more sensitive in picking up brain damage; that is something all of us ought to remember. I was surprised to hear of a series as long as this one without some effort being made to do psychologic tests. It has been my experience that we pick up organic brain damage with psychologic tests long before we pick it up with electroencephalography.

DR. CARLOS G. DEGUTIERREZ-MAHONEY: This problem is a very important one. This discussion gives me an opportunity to plead for recognition of, or at least an open mind to, the work that has been done regarding the pathology of concussion. To say we know nothing about the pathology or pathologic physiology of concussion is not quite true. If you will go back to the work of Jacob in 1913, you will learn that histologic changes have been found in concussion, findings supported in more recent times by Windle's work. My own studies have also shown that there are changes in the neuron, in the cell body itself, in the axis cylinder, and in the myelin sheath. When we deny these observations categorically, just because someone has said concussion is a state in which one cannot find cerebral changes, we are not opening our minds to the whole picture. If we add these histologic findings to what we know from psychological studies and to what we are learning from electroencephalography, we shall have a sounder understanding of what has appeared to be a nebulous matter.

DR. IRVING J. SANDS: This paper has dealt with a subject of great importance to all who work in neuropsychiatry, especially those who occasionally have to discharge medical-legal obligations. Electroencephalography has proved a valuable addition to the diagnostic armamentarium of the neuropsychiatrist. However, it has many limitations, and it is not an infallible instrument. Since it has been recognized that an electroencephalogram may be perfectly normal even in the presence of established brain injuries, its value has diminished. In fact, one hesitates to use it as a specific diagnostic means.

DR. ISRAEL STRAUSS: An electrocardiogram of a heart may be absolutely normal and yet the patient may die from cardiac disease. It is also true that occasionally an electrocardiogram will show pathologic changes in the heart that are not clinically diagnosable. This is also true of the brain electroencephalography, a point which has been brought out, I think, by what Dr. Hans Strauss has said. In 1934 a paper was read and published by Nathan Savitsky and myself on what was known regarding the pathology of concussion. You will find quite a historical résumé, from the time of Hippocrates up to the day we wrote that paper, with all the views of the pathologist, etc., on concussion.

DR. LEWIS D. STEVENSON: In any group of 100 patients selected as was this, a large number will have received no brain injury, no injury of any kind, and I wonder whether it is an assumption of Dr. Denker's that all these patients actually had concussion. It seems to me we have to have some clinical criteria for determining whether a man was injured or not, and such criteria were not mentioned. In any such group quite a percentage would be out-and-out malingerers, although that point was not brought out here.

DR. RICHARD M. BRICKNER: During the war Fulton observed that British railroad workers whose heads were caught between round disks on the ends of railroad trains showed no loss of consciousness, even though the head was terribly battered.

DR. PETER G. DENKER: In reply to Dr. Brickner's last remark, it is well recognized that if a person's head is stationary at the time of the injury to his head, he is less likely to suffer from postconcussion symptoms. This brings up the question as to the etiology of the postconcussion syndrome from a physiologic standpoint, as apart from the pathologic brain changes produced. In this respect you all know of the theory of Dr. Denny-Brown, who believes from his studies that there must be an acceleration factor, the brain being thrust forward within the skull at the time of injury. If the head is kept stationary, this acceleration is not produced, so that postconcussion symptoms do not result.

I did not state, or even imply, that the electroencephalogram should be the sole criterion in assessing the importance of brain damage or in ruling out neurosis or malingering. As in other conditions of medicine, I do feel, however, that the EEG is a very helpful laboratory aid which has to be considered in the total picture of evaluation.

DR. GERALD F. PERRY: On the question of interpretation of abnormal records there is considerable variation in different schools. Dr. Strauss mentioned that he did not think any records should be regarded as abnormal which had a frequency greater than 13 and voltage over 30 μv. The Gibbs and other schools define such a frequency as abnormal. Similarly, the amplitude asymmetry, present in two cases, was marked, and is clearly defined as abnormal by most schools of interpretation. Dr. Strauss is conservative in the interpretation of spikes, but we tried to encompass all views in the reading of our records. Besides, the spike activity seen in some of our cases is a part of the total abnormality present. Our cases did not give a history of epilepsy or of definite epileptic seizures.

Peripheral Nerve Pressure Syndrome with Conduction Block. DR. JOSEPH MOLDAVER.

In cases with tourniquet paralysis there is a disturbance in the function of the peripheral nerves which is due to the mechanical pressure on the nerves and is not the result of ischemia. The characteristics of this syndrome are as follows: The electrical studies show a typical block of conduction characterized by the lack of response to stimulation of the motor nerve above the injury and a good response below the injury. The conduction block is very well defined in tourniquet paralysis. When the stimulating electrode is moved slightly above or below the injury, there is no response or there is a good response to stimulation of the nerve. In addition, there is no tingling sensation when the sensory fibers are stimulated below the injury, but just above it the tingling elicited by electrical stimulation is felt and referred to the sensory distribution of the limb. These patients may show complete paralysis, and their condition might sometimes be taken for conversion hysteria because of the supposedly normal sensory findings. There is a dissociation of the sensations. Pain sensation is never lost, and there is often an actual hyperalgesia, that is, a low threshold for pain. The fibers subserving touch, pressure, vibration, and position sense are affected and often lost. Heat and cold sensibility is seldom impaired. The sympathetic fibers are not affected. Pilomotor reflexes are normal. Skin resistance also is normal, and the temperature of the skin is normal too.

In some cases with peripheral nerve pressure the findings may be the same. In cases with block of conduction affecting the motor fibers and resulting in a dissociation of the sensations there is no paresthesia or spontaneous tingling. The fibers responsible for the tingling sensation, therefore, show also a block of conduction.

DISCUSSION

DR. THOMAS I. HOEN: You must not be misled into thinking this contribution is not a really important one. This paper, being very objective and precise in its presentation, does not leave much room for controversial comment. It is quite possible that the impression Dr. Moldaver gave you that the loss of conductivity in the nerve was due to compression of the axon might not be true. We cannot perform a biopsy on a nerve to see what it looks like, but we have seen cases in which axons are compressed to 10% of their normal volume and have normal conductivity. In these cases there is an absolute paralysis, which Dr. Moldaver has shown you, and he has hypothesized that it is due to the reduction in volume of the axons. I am inclined to think the lesion may be not of the axons but of the myelin; it may produce a breakdown in myelin that may prevent passage of the impulse because of failure of insulation.

DR. RICHARD M. BRICKNER: Can Dr. Moldaver in any way relate this syndrome to spinal cord injuries which recover of themselves?

DR. I. M. TARLOV: Dr. Moldaver has presented evidence that mechanical deformation rather than ischemia causes compression paralysis of a peripheral nerve, in which there is apt to be preserved pinprick appreciation in the presence of motor paralysis and absence of position sense and vibration sense. I should like to cite a case which proves that ischemia may produce the same type of syndrome. My patient was injured in an automobile accident. She had complete paralysis of her right upper limb and absence of position sense and vibration sense, but she could feel pinprick applied to the limb. There was absence of radial and brachial artery pulsations on the paralyzed side, the syndrome having been caused by thrombosis of the subclavian artery. One may say, then, that ischemia may produce the same type of syndrome that Dr. Moldaver has described. One may occasionally find the same type of syndrome with spinal cord compression. Hence one sees patients with the primary lateral sclerosis syndrome, or the posterolateral syndrome, caused by spinal tumors.

DR. JOSEPH MOLDAVER: I think that in some cases the damage to the peripheral nerve can affect myelin sheaths, or sometimes the axons, but in other instances the lesion to the peripheral nerves may be very minimal or may be submicroscopic, as in certain cases the return of function is rather fast.

Ischemia cannot explain the conduction block that one sees in cases of tourniquet paralysis or of pressure paralysis. It is obvious that if a tourniquet has been applied the limb would be ischemic from the tourniquet down, and yet the damage that one sees is a very narrow one, very much confined to the area that has been constricted or pressed upon by the tourniquet itself. The excitability of the entire distal end in those cases remains normal; if ischemia were responsible for the lesion, there is no reason why damage to the distal end would not take place as well. It is obviously easy to assume that ischemia is responsible for the lesions, as one knows that a tourniquet is used to arrest the blood flow, but one forgets that a tourniquet is also an instrument that can cut deeply into the various structures, such as the skin, muscles, and nerves. Furthermore, in some of the experiments done on the animals there has been a definite constriction of the nerves that have been under pressure.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

CONGENITAL STATIONARY NIGHT BLINDNESS WITHOUT OPHTHALMOSCOPIC OR OTHER ABNORMALITIES. F. D. CARROLL and C. HAIG, A. M. A. Arch. Ophth. **50**:35 (July) 1953.

Carroll and Haig describe night blindness present at birth, stationary, occurring in an approximately equal number of males and females, and with no associated abnormalities. Nineteen pedigrees of this disease had previously been reported by Bell. The authors describe a family with this form of congenital stationary night blindness. Dark-adaptation tests, absence of the Purkinje phenomenon, electroretinography, and clinical studies indicated a complete lack of rod function. An unusual opportunity was thus presented for the study of the visual capacity of persons who have normal (or almost normal) cone function only. In peacetime these people are occasionally embarrassed by their handicap, but they marry, have children, and lead almost normal lives; in wartime, however, it is important for the ophthalmologist to recognize the condition so that those affected will not be so placed that their disability may endanger themselves or others.

SPAETH, Philadelphia.

CEREBRAL EFFECTS OF EXPERIMENTAL HYPOTHERMIA. J. C. CALLAGHAN, D. A. MCQUEEN, J. W. SCOTT, and W. G. BIGELOW, A. M. A. Arch. Surg. **68**:208 (Feb.) 1954.

In 17 experiments, 10 Macacus rhesus monkeys were cooled by immersion to 20 C. (68 F.) and then rewarmed to normal body temperature (in some instances by means of radiofrequency). Cooling produced a slowing of the cardiac and respiratory rates, with progressive loss of consciousness, motor power, and reflex activity. The electroencephalograms showed progressive reduction of cortical potentials, with practically complete extinction of electrical activity at 20 C.

After rewarming, all functions, including the electroencephalographic potentials, returned to normal. The cooling had no effect on the aptitude with which the animals subsequently performed tests learned prior to the experiment. The authors conclude that in rhesus monkeys, reduction of body temperature to 20 C. appears to have no permanent ill effect on cerebral function.

LIST, Grand Rapids, Mich.

EFFECT OF ORAL ADMINISTRATION OF COMBINATIONS OF PENTYLENETETRAZOL AND BARBITURATES. T. KOPPANYI and J. F. FAZEKAS, Am. J. M. Sc. **226**:265 (Sept.) 1953.

This investigation in dogs and humans was to ascertain whether the simultaneous oral administration of pentylenetetrazol and barbiturates resulted in a counteraction of the two drugs. It was found that the administration of pentylenetetrazol to dogs in oral doses of 35 up to 100 mg. per kilogram of body weight caused proportionately increasing neurologic stimulation up to the point of convulsions. Stimulation lasted for three to eight hours. Doses of 35 mg. of pentobarbital per kilogram produced surgical anesthesia, but when administered with 100 mg. of pentylenetetrazol per kilogram, the animals did not sleep. Comparable antagonistic effects were found between pentylenetetrazol and phenobarbital sodium. Humans ingesting up to 45 mg. of pentylenetetrazol per kilogram of body weight developed central nervous system stimulation and exhibited excitement, olfactory hallucinations, nausea, vomiting, and clonic convulsions. Doses of 200 mg. of phenobarbital, pentobarbital, or secobarbital sodium administered with 300 to 600 mg. of pentylenetetrazol did not alter the hypnotic effect of the barbiturates. Subjects given larger doses of barbiturates, up to 15 mg. per kilogram of body weight, combined with pentylenetetrazol, 45 mg. per kilogram of body weight, showed delay of onset of sleep, restlessness, and retching within three hours following administration. Subjects who fell asleep could be aroused easily. Pentylenetetrazol administered with barbiturates prevented the onset of anesthesia resulting from barbiturates and saved the lives of animals and humans.

BERLIN, Mount Vernon, N. Y.

ON THE RELATIONSHIP OF URINARY COPPER EXCRETION TO THE AMINOACIDURIA IN WILSON'S DISEASE (HEPATOLENTICULAR DEGENERATION). L. L. UZMAN, Am. J. M. Sc. **226**:645 (Dec.) 1953.

A case of hepatolenticular degeneration manifesting persistent massive aminoaciduria was studied to ascertain the relationship of the aminoaciduria to cupruria. The amino acids excreted were preponderantly threonine, arginine, asparagine, and alanine. The cupruria showed considerable variation and bore no direct relationship to the magnitude of the aminoaciduria. The urinary copper was isolated in the form of a complex with oligopeptides of a specific nature. Uzman suggests that the oligopeptide-copper chelate represents the form in which copper passes from the glomerular filtrate, and that the urinary excretion of the metal is a result of the competition for tubular resorption between the oligopeptide complex and amino acids present in high concentration in the tubular fluid.

BERLIN, Mount Vernon, N. Y.

VESTIBULAR MECHANISMS OF FACILITATION AND INHIBITION OF CORD REFLEXES. B. E. GERNANDT and C. A. THULIN, Am. J. Physiol. **172**:653 (March) 1953.

Gernandt and Thulin studied the effect of impulses elicited by adequate stimulation of the vestibular organ on the ventral horn cells, using the monosynaptic method of testing. The impulses are transmitted by the vestibulospinal and reticulospinal tracts from centers some of which are facilitatory (increasing muscle tone via vestibulospinal and reticulospinal tracts) and some inhibitory (decreasing muscle tone by way of other reticulospinal tracts). Decerebrated, decerebellated cats were used. It has been demonstrated that even in the resting state a spontaneous stream of impulses always traverses the vestibular nerve, sufficient usually to make vestibular facilitatory activity apparent. Either ipsilateral or contralateral sectioning of the vestibular nerve resulted in approximately the same degree of reduction of facilitatory influx upon the tonic activity of spinal reflexes. The spinal reflexes are influenced by adequate vestibular stimulation as follows: Stimulation of, for example, the horizontal canals by rotation facilitates the monosynaptic test reflex, the more the speed of rotation is increased; when rotation is suddenly arrested, there is, because of inertia, an opposite flow of the endolymph, with resulting inhibition of the impulse discharge of the eighth nerve. The degree of facilitation or inhibition is related to the speed of angular acceleration; the same applies to the postrotatory effect. The facilitation and inhibition of the monosynaptic test response of an extensor nerve during vestibular stimulation were demonstrated to be just the opposite of that induced in the nerve to the flexor muscle. The previous inhibitory direction of rotation became facilitatory, demonstrating a reciprocity which indicated that certain mononeurons are inhibited while their immediate antagonists are excited, but the manner is not yet understood. This reciprocity is lost when the eighth nerve is cut on one side, and it cannot be demonstrated unless the decerebrate animal is in excellent condition.

BERRY, Washington, D. C.

NATAL DAY DEATHS. H. N. BUNDESEN, J. A. M. A. **153**:466 (Oct. 3) 1953.

In a study based on data on 10,000 neonatal deaths, Bundesen points out that to reduce needless infant deaths, most effort must be concentrated on the first three days of life and on infants of low weight, who die mainly from abnormal pulmonary ventilation and injuries at birth.

According to this study, there are seven major anatomic causes of death in the neonatal period: (1) abnormal pulmonary ventilation, (2) injuries at birth, (3) malformations, (4) infections, (5) blood dyscrasias, (6) anoxia, and (7) miscellaneous causes. Abnormal pulmonary ventilation and birth injuries were responsible for 83.5% of all the deaths on the first day in infants of low weight (under 1,500 gm.) in this series.

As a result of this analysis of the causes of death and the factors contributing to them in these infants, it is pointed out that concentration of effort is required, with complete cooperation of the patient, in improving prenatal care of women of low socioeconomic status, in constantly providing for skillful natal care of the mother in the hospital by obstetricians, and in providing for optimal postnatal care of the infant by pediatricians.

ALPERS, Philadelphia.

ENZYMATIC ESTERIFICATION OF ALPHA-GLYCEROPHOSPHATE BY LONG-CHAIN FATTY ACIDS. A. KORNBERG and W. E. PRICER JR., J. Biol. Chem. **204**:345 (Sept.) 1953.

Some time ago it was demonstrated that such simple units as choline and phosphate are incorporated into phospholipid fractions by cell-free preparations. L-alpha-glycerophosphate is a precursor in the enzymatic synthesis of a phospholipid, probably phosphatidic acid. Kornberg and Pricer now present evidence that the formation of the diacylphosphatidic acids proceeds by esterification of the α-glycerophosphate with the activated acyl coenzyme A derivatives of the higher fatty acids. This synthesis has been demonstrated indirectly, starting with adenosinetriphosphate (ATP), coenzyme A (CoA), and fatty acid, and directly from palmityl CoA synthesized chemically or enzymatically. Thus, in the presence of a liver enzyme and catalytic quantities of CoA esterification of α-glycerophosphate by two moles of a higher fatty acid occurred with concomitant conversion of 2 moles of ATP to inorganic pyrophosphate and adenosine-5′-phosphate. Straight-chain fatty acids with 16, 17, or 18 carbon atoms were far more effective than shorter- or longer-chain acids in the esterification.

PAGE, Cleveland.

DIRECT DETERMINATION OF PHOSPHATIDYL ETHANOLAMINE AND PHOSPHATIDYL SERINE IN PLASMA AND RED BLOOD CELLS. J. AXELROD, J. REICHENTHAL, and B. B. BRODIE, J. Biol. Chem. **204**:903 (Oct.) 1953.

Cephalins may be estimated in plasma and red blood cells by extraction, hydrolysis, and formation of colored derivatives of ethanolamine and serine with dinitrofluorobenzene. They are separated by differential solubilities and measured spectrophotometrically. The specificity of the methods has been determined by countercurrent distribution. Phosphatidyl ethanolamine and phosphatidyl serine are present in plasma of both man and dog in small amounts, while red blood cells contain considerable amounts.

PAGE, Cleveland.

MICRODETERMINATION OF PURINE NUCLEOSIDE PHOSPHORYLASE ACTIVITY IN BRAIN AND ITS DISTRIBUTION WITHIN THE MONKEY CEREBELLUM. E. ROBINS, D. E. SMITH, and R. E. MCCAMAN, J. Biol. Chem. **204**:927 (Oct.) 1953.

Purine nucleoside phosphorylase activity of as little as 3 γ of brain could be determined by a differential spectrophotometric method. In monkey cerebellum the granular layer has a very high enzymatic activity. The white matter also has high activity; oligodendroglia or axis cylinders are sites of very high rates of purine nucleoside phosphorylase activity. The enzymatic splitting of inosine in brain is entirely phosphorolytic. Synthesis of hypoxanthine deoxyriboside from hypoxanthine and deoxyribose-1-phosphate has been shown, using partially purified enzyme from brain.

PAGE, Cleveland.

BIOSYNTHESIS OF SPHINGOSINE: UTILIZATION OF CARBOXYL-LABELED ACETATE. I. ZABIN and J. F. MEAD, J. Biol. Chem. **205**:271 (Nov.) 1953.

Derivatives of sphingosine isolated from brain of weanling rats fed carboxyl-labeled acetate were found to contain the tracer. Degradation of the dihydrosphingosine derivative showed that carbon atoms 1 and 2 contained no tracer. The distribution in the rest of the compound suggests that a 16-carbon, fatty-acid-like intermediate is involved in the biosynthesis of sphingosine.

PAGE, Cleveland.

SEQUENCE OF AMINO ACIDS IN OXYTOCIN, WITH A PROPOSAL FOR THE STRUCTURE OF OXYTOCIN. V. DU VIGNEAUD, C. RESSLER, and S. TRIPPETT, J. Biol. Chem. **205**:949 (Dec.) 1953.

It had previously been shown that oxytocin hydrolysates contain leucine, isoleucine, tyrosine, proline, glutamic acid, asparic acid, glycine, and cystine in equimolar ratios to each other. Evidence is now presented for a tentative structure for this principal uterine-contracting and milk-ejecting hormone of the posterior pituitary gland.

PAGE, Cleveland.

A Study of Inositol-Containing Lipides. J. N. Hawthorne and E. Chargaff, J. Biol. Chem. **206**:27 (Jan.) 1954.

Ox brain inositol phosphatides hydrolysates yield inositol diphosphate and a more complex substance, probably a diester. Mesoinositol is almost ubiquitous and may be an essential cell constituent.

Page, Cleveland.

Paper Chromatography of Lecithins. F. M. Huennekens, D. J. Hanahan, and M. Uziel, J. Biol. Chem. **206**:443 (Jan.) 1954.

A series of compounds, derived from unsaturated lecithin (dipalmitoleyl)-L-α-glycerylphosphorylcholine, have been prepared and then identified by means of paper chromatography by using various alcohol-water mixtures as the solvent systems. Spray techniques have been employed to detect phosphate, choline ester, and unsaturated groupings.

Page, Cleveland.

Effect of Direct Suggestion on Pain Sensitivity in Normal Control Subjects and Psychoneurotic Patients. W. P. Chapman, J. E. Finesinger, and G. Chesley, J. Nerv. & Ment. Dis. **118**:19 (July) 1953.

The effect of suggestion was studied in 15 female college students and 16 psychoneurotic patients. The Hardy-Wolff-Goodell heat radiation apparatus was used to ascertain the stimulus intensity at which the heat stimulus was perceived as painful and the stimulus that evoked a wince reaction. Verbal suggestion alone and the administration of placebos reinforced by verbal suggestion were used. In the group of subjects as a whole, neither the threshold of pain perception nor the threshold for the pain reaction were altered significantly by techniques of suggestion.

Two patients with the diagnosis of hysteria and one control subject showed elevation of pain thresholds following suggestion. Changes in pain perception level were not the rule, and incidence of change was only slightly greater in the neurotic patients than in the control subjects.

Berlin, Mount Vernon, N. Y.

Antidromic Impulses in the Dorsal Roots. J. S. Habgood, J. Physiol. **121**:264 (Aug.) 1953.

In 1935, Barron and Matthews described antidromic impulses in the dorsal roots and postulated the existence of "recurrent fibres." This concept has been reinvestigated in experiments on cats, rats, and frogs.

Recordings have been made from dorsal rootlets, cut peripherally, during repetitive stimulation of the sciatic nerve. The large irregular bursts of impulses thus evoked gradually die away and reveal a few with a constant delay.

This delay has been measured after making due allowance for conduction within the cord; in almost all cases there is a residual, unexplained delay in the cord of 2 to 3 msec. It has therefore been concluded that the impulses have been conducted in at least two neurones. "Recurrent fibres," if they exist at all, seem to be extremely rare.

The vast majority of antidromic discharges may be divided into three groups:

(*a*) Irregular discharges, the "dorsal root reflexes," probably generated by the dorsal root potential and evoked by synchronous afferent volleys.

(*b*) Regular discharges of "recurrent impulses," evoked by activity in only one or two afferent fibers and probably occurring only in rare cases when the conditions favoring interaction are especially good.

(*c*) Secondary neurone discharges, similar to (*b*), but evoked mainly by intraspinal activity.

There is evidence to suggest that the occurrence of all these impulses is of only secondary physiological importance.

Thomas, Philadelphia.

SMALL-NERVE JUNCTIONAL POTENTIALS: DISTRIBUTION OF SMALL MOTOR NERVES TO FROG SKELETAL MUSCLE, AND THE MEMBRANE CHARACTERISTICS OF THE FIBERS THEY INNERVATE. S. W. KUFFLER and E. M. VAUGHAN WILLIAMS, J. Physiol. **121**:289 (Aug.) 1953.

The large and small fibers of the motor nerves in the frog innervate two different sets of muscle fibers. The large fibers cause propagated impulses in fast-contracting muscle fibers (the "twitch system"), and the small fibers cause nonpropagated electrical changes and localized contraction in slowly contracting muscle fibers (the "small nerve system"). The electrical changes in the muscle caused by stimulating the latter group are described as small junction potentials; their properties were investigated in this study. By an ingenious method utilizing anodal block of rapidly conducted impulses, the small, slow-conducting fibers only were effectively stimulated in the ventral roots.

The resulting composite small junction potentials rise in a few milliseconds to a peak depolarization of 7 to 15 mv., and the restitution takes place along an approximately exponential time course with a half-time of 23 to 39 msec. and leads into a phase of hyperpolarization (positive after-potential). The latter phase reaches 20 to 50% of the depolarization peak. The whole potential complex may last up to 0.4 second at 20 to 24 C. The effect on the muscle of single impulses at single junctions is small and localized; the local effect can be increased by summation of repetitive stimuli. Each muscle fiber is supplied with multiple junctions distributed throughout its length, so that repetitive stimulation of the small nerve fibers leads to a respectable increase in tension in the muscle fibers. A detailed study was made leading to many interesting observations that cannot be included in an abstract. The small nerve system was not found in mammalian muscle.

A simple electrical model which reproduces many features of the small junction potentials is described.

THOMAS, Philadelphia.

EFFECT OF INHIBITORY NERVE IMPULSES ON A CRUSTACEAN MUSCLE FIBER. P. FATT and B. KATZ, J. Physiol. **121**:374 (Aug.) 1953.

Experiments were made to study the effect of single excitor and inhibitor nerve fibers on the membrane of single crustacean muscle fibers.

An inhibitor impulse reduces the amplitude of the "end-plate potential," owing to a subsequent motor nerve impulse. This effect is observed when the interval between the antagonistic impulses is less than about 20 msec.

When the inhibitor impulse arrives during the falling phase of the end-plate potential, it accelerates the decay of the end-plate potential.

A "direct" effect of the inhibitor impulse on the resting membrane potential of the muscle fiber is not usually seen. However, when the membrane potential has been displaced in either direction, by means of an applied current, the inhibitor impulse produces a potential change which is directed toward the normal resting level.

This action, and the acceleration of decay of the end-plate potential by the inhibitor impulse, can be explained by a lowering of the membrane resistance of the muscle fiber, more specifically of the resistance in series with the resting electromotive force.

All the electrical effects of the inhibitor impulse are compatible with the concept of a single inhibitor-receptor reaction ($I + R \rightleftarrows IR$), which changes the ion permeability of the fiber membrane and, at the same time, competes with the action of the excitatory transmitter ($E + R \rightleftarrows ER$) on the common receptor molecule.

THOMAS, Philadelphia.

STUDIES ON THE CERVICAL SPINAL CORD OF MAN. B. BOSHES and F. PADBERG, Neurology **3**:90 (Feb.) 1953.

When a patient experiences the loss of ability to recognize by palpation the form and nature of an object, that defect is usually called "astereognosis." Assuming that the palpating part has relative integrity of motor power and preservation of the modalities of touch, temperature, and pain, the disability is usually ascribed to a lesion of the contralateral parietal lobe. The authors point out that this thinking has resulted in many mistaken diagnoses, often in cases amenable to surgical intervention.

The material studied consisted of eight anatomically verified cases of cervical cord lesions (seven tumors and one syringomyelia), in all of which there was a disturbance in one or more phases of deep sensibility or its recognition. In contrast, one case of thalamic tumor and one of verified parietal lobe tumor are also presented. The usual tests for deep and superficial sensations were employed in the study. In addition to testing the affected limb for object recognition, the authors also utilized the numeral or figure-writing test.

It was found that interruption of the posterior columns at a high cervical level produces profound disturbances in deep sensibility in one or both of the upper limbs. The authors recommend that the spatial appreciation defect so produced be called stereoanesthesia, since the defect is in conduction, and that the term astereognosis be used exclusively to designate instances in which there is no defect in conduction, as in parietal lobe lesions.

It was also found that high cervical stereoanesthesia is usually accompanied by loss of pallesthesia and kinesthesia, but graphesthesia may be preserved. Thalamic lesions obliterate or disturb all modalities of exteroceptive sensation; hence pallesthesia, kinesthesia, and graphesthesia may be preserved. Parietal cortex lesions affect functions dependent on spatial orientation; hence they produce a loss of figure-writing interpretation (graphagnosis or agraphognosis) and loss of object-in-space recognition (astereognosis), while a nonspace orienting function, vibration sense, is spared.

ALPERS, Philadelphia.

BACKGROUND ILLUMINATION AND THE VISUAL THRESHOLD IN HEMIANOPIC AREAS. M. B. BENDER and H. P. KRIEGER, Neurology **3**:102 (Feb.) 1953.

In a previous investigation the authors demonstrated that changing the illumination of the background affected the perception of the target located in the so-called hemianopic field. The present study is an attempt to quantify the relationship between background illumination and target perception.

The study was carried out on two hemianopic patients. The first had a surgically removed subdural hematoma. Before operation there was a right third nerve paralysis and a left homonymous hemianopsia. Postoperatively the hemianopsia remained. The retinas were at all times normal. The second patient presented a mild right-sided paresis and bilateral hyperreflexia. A right-sided subdural hematoma was removed surgically. Postoperatively, a left homonymous hemianopsia was found; all other signs disappeared. Ophthalmoscopic examination revealed no retinal pathology.

The authors describe their experimental methods and illustrate their findings graphically. They found that these patients with an homonymous hemianopsia, when examined under daylight illumination, could see a small luminous target in these apparently blind areas, provided the background illumination was almost eliminated. Raising the illumination of the background was found to raise the differential threshold in apparently hemianopic areas, as measured with a luminous target in a dark room. The degree of rise in the differential threshold was the same in both the normal and the defective areas, except that in the anopic areas a critical point was found beyond which a rise in the background illumination resulted in subjective disappearance of the target. After removal of the background illumination, the rate of dark adaptation was found to vary inversely with the intensity of the preceding background illumination. This was true of both normal and abnormal areas of the field of vision.

These results are considered in relation to the difference in absolute threshold between the normal and the defective half-fields and interpreted in terms of simultaneous stimulation of analogous normal and defective sensory fields and in terms of figure-ground relationships.

ALPERS, Philadelphia.

RADIOACTIVE ARSENIC AND THE PREOPERATIVE DETECTION OF CEREBRAL TUMORS. P. BENDA, M. DAVID, and J. CONSTANS, Rev. neurol. **89**:101, 1953.

Radioactive arsenic supplied as ammonium arsenate, with at least 20 mc. per milligram by weight of AS, was injected intravenously. Measurement of the radioactivity was begun two hours after the injection, and comparable areas on the two sides of the head were counted. It was found that the ratio of radioactivity in healthy cerebral cortical tissue to the site of tumor

tissue was 1:35 for meningiomas, 1:7 for neurinomas, and 1:17 for an astrocytoma. The 0.1 to 0.3 mg. of AS injected is nontoxic, and a great part of it is excreted in three hours.

BERLIN, Mount Vernon, N. Y.

Meninges and Blood Vessels

TUBERCULOUS MENINGITIS IN INFANTS AND CHILDREN. A. ROBINSON and Y. HA RO, A. M. A. Am. J. Dis. Child. **87**:139 (Feb.) 1954.

Robinson and Ha Ro review a series of 25 children with tuberculous meningitis. Positive skin tests were observed in 92%, and pulmonary tuberculosis was demonstrated by roentgenography in 96%. All patients received streptomycin intramuscularly until three months after the cerebrospinal fluid was normal, streptomycin intrathecally until the spinal fluid was normal, and *p*-aminosalicylic acid (PAS). Some received thiazolsulfone, and others isoniazid. Streptokinase and purified protein derivative (PPD) were occasionally given intrathecally to those with subarachnoid block. All components of the cerebrospinal fluid began to improve between two and four months and were normal by the eighth month.

The problem of block in the circulation of the spinal fluid was a difficult one. The following were interpreted as evidence of block: (1) a rising spinal fluid protein; (2) marked difference between the protein content of the lumbar spinal fluid and that of the cisternal or ventricular fluid, and (3) developing hydrocephalus. Of several methods of treatment, intracisternal or intraventricular instillation of streptomycin seemed the most helpful. In this series streptokinase (four patients) and PPD (seven patients) did not appear to be of value. Autopsy revealed that none of the cases so treated showed any unusual findings that could be attributed to these agents.

Sixty per cent of the patients were alive for at least six months. There was no correlation between the length of interval from onset to treatment and the mortality. However, patients with a clear sensorium on admission had a distinctly better prognosis, both as to life and as to residual neurologic deficits.

Of the 15 still alive, 4 show evidence of severe neurologic damage; 3 other patients had minor changes. Four of the survivors developed definite hydrocephalus. Many of the patients showed some degree of mental retardation. The diagnosis has been complex because of the depressive state seen in children hospitalized for long periods. A position of play supervisor was created to carry out daily organized play activity. The use of physiatric care is also stressed.

SIEKERT, Rochester, Minn.

OCCLUSION OF THE SUPERIOR CEREBELLAR ARTERY. J. A. LUHAN and S. L. POLLACK, Neurology **3**:77 (Feb.) 1953.

Luhan and Pollack report six instances of the syndrome of occlusion of the superior cerebellar artery. The first three cases were clinically obvious without necropsy confirmation. The fourth patient was studied only pathologically; the focal neurologic symptoms arose in the course of subacute bacterial endocarditis. The fifth patient suffered from the effects of very extensive encephalomalacia in the distribution of one middle cerebral artery, and only by previous findings could it have been recognized that the softening in the distribution of the superior cerebellar artery found at necropsy had preceded the more massive cerebral insult. The sixth case was a complicated one, manifested at its onset by initial apoplectiform symptoms simulating those associated with rupture of a basilar intracranial aneurysm. Upon examination sometime later, there was found, in addition, a syndrome typical of occlusion of the superior cerebellar artery.

This condition is characterized by a distinctive clinical syndrome: sudden onset without loss of consciousness, marked usually by vomiting, often by dizziness, and by inability to stand or walk; ipsilateral cerebellar dysfunction, particularly tremor of intention, and usually Horner's syndrome on the side of the lesion; loss of pain and temperature sense or subjective numbness in the total contralateral distribution; sometimes contralateral impairment of mimetic facial innervation, and inconstant occurrence of nystagmus and hearing loss, not clinically reliable as indices of lateralization.

These symptoms arise because of interruption of the brachium conjunctivum, the lateral spinothalamic and quintothalamic pathways, descending oculosympathetic fibers, and sometimes the lateral lemniscus and median longitudinal fasciculus in the tegmentum of the rostral pons. The necropsy findings of three of the cases in this series are described.

ALPERS, Philadelphia.

SPINAL FLUID FINDINGS FOLLOWING CEREBRAL ANGIOGRAPHY. J. M. STEIN and M. FINK, Neurology **3**:137 (Feb.) 1953.

Spinal fluids from 21 patients were examined prior to and after angiography. Lumbar punctures prior to angiography were done at various intervals, but all punctures following angiography were performed between 12 and 24 hours after the procedure. In each instance the spinal fluid was examined for color, cell count, and total protein content.

All angiograms were percutaneous, using 35% iodopyracet (Diodrast) as the contrast medium. Maximal iodopyracet injection was 70 ml. at one procedure. While the majority of patients were subjected to unilateral carotid punctures, bilateral punctures were done in four, and combined bilateral carotid and vertebral punctures in one patient.

It was found that neither a marked pleocytosis nor a marked increase in protein content of the spinal fluid is a usual concomitant of iodopyracet angiography. It may be concluded that when such spinal fluid changes are found, they are unrelated to the procedure.

ALPERS, Philadelphia.

Diseases of the Brain

CONVULSIVE EFFECTS OF LIGHT STIMULATION IN CHILDREN. R. G. BICKFORD, D. DALY, and H. M. KEITH, A. M. A. Am. J. Dis. Child. **86**:170 (Aug.) 1953.

Bickford, Daly, and Keith report observations on 27 children with epilepsy who were sensitive to flickering light. Some had attacks after exposure to the flickering light encountered in daily life, such as in motoring through an avenue of trees when the sun is low. Others gave clinical or encephalographic epileptic responses to flickering light which could be produced only under laboratory conditions. The authors suggest that three separate classes of patients can be recognized: (1) a clinically sensitive group, in which light of the intensity encountered in daily life is capable of inducing clinical attacks; (2) a less sensitive group, in which clinical seizures can be induced only under laboratory conditions of high intensity of illumination and a rapid flicker, and (3) children in whom the only evidence of sensitivity is the occurrence of a seizure discharge in the electroencephalogram when stimulated by light and unaccompanied by any detectable clinical evidence of a seizure. Patients may shift from one group to another, as indicated by day-to-day testing. There is no diagnostic encephalographic pattern of this condition. In the resting record, the commonest type of abnormality is the diffuse, high-voltage, 3-per-second spike-wave discharge, which was seen in about 75% of the group. Some showed focal sharp-wave discharges confined to the occipital regions. The usual type of discharge produced by the stimulation of flickering light was a diffuse spike-wave, which might have the classic 3-per-second configuration, or more commonly was a distorted, atypical variety. The most effective flash frequencies were found to lie between 10 and 20 cps. Myoclonic jerking was found to be closely related to spike discharges in the electroencephalogram. Arrest of speech and turning of head and eyes were variable and inconstant in their relationship to spike discharges. Possible underlying mechanism and hypothetical pathways are discussed. The participation of a diffuse thalamocortical system seems likely. Certain anticonvulsant drugs given intravenously could reduce the sensitivity to flickering light, but the effect was brief and it did not necessarily parallel the clinical result over an extended period. For certain patients, the wearing of darkly tinted or polaroid spectacles has been effective in preventing attacks.

SIEKERT, Rochester, Minn.

REACTIONS FOLLOWING ANTIRABIES PROPHYLAXIS. N. H. BLATT and M. H. LEPPER, A. M. A. Am. J. Dis. Child. **86**:395 (Oct.) 1953.

Complications, particularly neuroparalytic accidents, occurring as a result of the administration of rabies vaccine continue to constitute a real problem. Reactions severe enough to cause referral were seen in 15 of 2,193 persons inoculated by the Chicago Board of Health, a ratio of 1:146, or 0.7%. Eight patients showed only transient febrile reactions without nervous system signs, although some had subjective complaints. Seven patients, a ratio of 1:313, or 0.3% showed a reaction with neurologic signs.

The patients with neurologic involvement became ill after the 4th to the 14th injection. All had fever, which usually lasted longer than three days. The length of fever apparently does not completely correlate with the severity of the disease. Symptoms included headache, malaise, weakness, radicular pain, anorexia, emesis, and faintness. The signs included meningeal irritation, weakness or paralysis of the extremities, positive Babinski response, dysuria, and sensory disturbances, usually in the lower extremities. Permanent residuals, seen in three patients, consisted of weakness of the legs with sensory disturbances. One patient died. The occurrence of any unexplained fever or symptom is cause for discontinuance of the injections.

The cerebrospinal fluid contained from 15 to 1,120 cells per cubic millimeter, with an early predominance of lymphocytes. The protein was elevated in all but two patients, the highest initial value being 175 mg. per 100 cc.

Three patients with the most serious complications were treated with corticotropin. Two responded well. The authors suggest that corticotropin therapy might have been effective, although this is not proved.

An intradermal skin test, using diluted vaccine, was found to be positive in all patients with reactions. However, it was also positive in 60% of all the persons vaccinated, with complications or not. It is negative in persons not vaccinated.

SIEKERT, Rochester, Minn.

EPENDYMOMA OF THE FOURTH VENTRICLE IN AN INFANT UNDER ONE YEAR OF AGE. J. E. MAISEL and S. S. LAMM, A. M. A. Am. J. Dis. Child. **86**:604 (Nov.) 1953.

An 11-month-old girl was seen because of a stiff neck of one day's duration. Several days previously the child had become lethargic and unresponsive to environmental stimuli. Though awake, the infant appeared to be unaware of the surroundings, and she responded poorly to stimuli. The neck was stiff, but the Kernig and Brudzinski reflexes were absent. The anterior fontanel bulged slightly. A left internal strabismus was said to have been present since birth. There was ptosis of the right eyelid. A partial right-sided peripheral facial paralysis was noted. The tongue deviated obliquely to the right. The examination was otherwise normal save for a questionable Babinski reflex on the right.

The spinal fluid was clear and contained 300 cells per cubic millimeter, predominantly neutrophiles, and 52 mg. of protein, 50 mg. of sugar, and 702 mg. of chlorides, per 100 cc. Smears and culture were negative. X-ray of the skull showed some separation of the sutures.

Two days after admission the infant had a generalized convulsion and died within 10 hours. Autopsy disclosed a mass occupying the midportion of the cerebellum, filling the fourth ventricle, and extending into the brain stem. There was dilatation of the ventricular system. Microscopic diagnosis was ependymoma.

SIEKERT, Rochester, Minn.

NEUROGENIC STRIDOR IN INFANCY. R. J. ALLEN, H. A. TOWSLEY, and J. L. WILSON, A. M. A. Am. J. Dis. Child. **87**:179 (Feb.) 1954.

The authors believe that in certain instances in infancy the symptoms of stridor, apnea, and cyanosis can be precipitated by a neurogenic mechanism differing from "idiopathic convulsions" by the presence of a "trigger mechanism," which when stimulated reproduces the attacks. In the first case all attacks were precipitated by visceral stimulation, such as feeding, and "a type of convulsion" consisting of choking and respiratory difficulty occurred. These attacks responded to treatment with phenobarbital and diphenylhydantoin. The other infant had periods of respiratory distress. It was noted that pressure on the carotid sinus caused marked bradycardia,

dyspnea, and cyanosis. Treatment with belladonna appeared to abort the attacks. Infants with tracheoesophageal fistulae may react with episodes of dyspnea and cyanosis, particularly on stimulation of the trachea or the esophagus. A reflex is postulated, but the reason for the abnormal sensitivity in some infants is unknown.

SIEKERT, Rochester, Minn.

CONTROLLED SEARCH FOR NEUROLOGICAL DISTURBANCE ASSOCIATED WITH ASTEROL APPLICATIONS. J. HOLOWACH, J. L. O'LEARY, and D. L. THURSTON, A. M. A. Am. J. Dis. Child. **87**:261 (March) 1954.

Extensive laboratory and clinical studies have proved that 5% Asterol (2-dimethylamino-6-[β-diethylaminoethoxy]-benzothiazole) dihydrochloride is an effective topical remedy for tinea capitis. Sporadic reports of neurological disturbances related to its use prompted this investigation into the neurotoxic properties of this drug. Thirty-seven patients were studied with neurological and encephalographic studies before, during, and after the administration of Asterol. The ages ranged from 16 months to 12 years. Fourteen patients (38%) showed pretreatment encephalograms which were considered to be outside the normal range of their ages. The remaining had normal encephalograms. The series included six with a positive family history of convulsions; each of two patients had had one convulsion. The length of application of Asterol varied from 4 to 22 weeks. One patient in the group with an abnormal control electroencephalogram developed visual hallucinations a month after onset of therapy. With discontinuance of therapy these disappeared, and a later EEG was normal. Asterol was reapplied, without any further difficulty. Of the 23 patients who showed records normal for their ages prior to the use of Asterol, 1 developed changes in the EEG without clinical symptoms and another developed hallucinations with mild dysrhythmia in the EEG. The hallucinations in the latter patient also decreased rapidly after discontinuance of the drug, and renewed use of Asterol produced no untoward clinical signs or symptoms. There was essentially no change in the EEG.

Some authors have calculated that the incidence of neurotoxicity ranges from 1 per 500 patients to 1 per 1,000. Although the authors indicate that the group was too small to demonstrate conclusively whether Asterol has neurotoxic properties, they believe that the findings indicate the necessity of considering several significant factors in future studies, particularly the importance of pretreatment electroencephalograms if convulsive manifestations are to be evaluated conclusively, for in the present series 38% of pretreatment EEG's showed activity outside the normal range.

SIEKERT, Rochester, Minn.

A TYPE OF PARALYSIS OF CONJUGATE GAZE (OCULAR MOTOR APRAXIA). D. G. COGAN and R. D. ADAMS, A. M. A. Arch. Ophth. **50**:434 (Oct.) 1953.

The inability to turn the eyes fully in one or more directions resulting from a supranuclear lesion is called paralysis of conjugate gaze. The most familiar type is the simple paralysis of conjugate gaze, resulting from a cerebral or brain stem lesion, in which the eyes cannot be induced to move to one or both sides by any stimulus other than that arising in the labyrinth. Next, there is the so-called dissociated paralysis of gaze, in which there is unequal involvement of movements on command and on following stimuli. Then there is a type of paralysis due to basal ganglion or tectal disease, in which all control of the eyes for vertical movements is lost except for those movements associated with the labyrinthine, or lid-closing, reflex. This type has no specific name—indeed, it may be a variant of the simple paralysis of conjugate gaze, already referred to. It has generally been classified with the broad and ill-defined group of disorders known as pseudo-ophthalmoplegias. Finally, there is a little recognized abnormality of conjugate gaze which has been called ocular motor apraxia, in which willed movements of the eyes are impaired but random movements are retained.

The term ocular motor apraxia connotes a disturbance in which willed movements cannot be integrated toward a purposeful act, although the movements can be individually executed. Thus, in ocular motor apraxia the eyes cannot be rotated in the desired direction, though full movements may be carried out at random. Ocular motor apraxia differs from the simple paralysis of conjugate gaze chiefly in the preservation of random movements in ocular apraxia and in the fact that effort tends to overcome the defect in the simple ocular motor paralyses, whereas it tends to inhibit movement in the apractic disorder.

Cogan and Adams report two cases of ocular motor apraxia. The underlying pathology in the two instances was different. In the first case the disease was the result of postpartum thrombophlebitis, with, presumably, a thrombosis of the anterior half of the sagittal sinus, and probably of the cerebral veins as well. The cause in the second case was a rapidly advancing tumor of the right parietal and posterior frontal regions, probably involving the corpus callosum.

"The simple paralysis of conjugate gaze that results from unilateral cerebral lesions is usually transient, and recovery occurs within a few hours after restoration of consciousness. There is impairment of both voluntary and random movements of the eyes; and it is noteworthy that the harder the patient tries to turn the eyes, the more effective is the act. The same applies in general to the more lasting paralyses of brain-stem origin. With ocular motor apraxia, on the other hand, the random movements are relatively well retained or may be normal; the harder the patient tries to turn his eyes in the desired direction, the more he is unable to do so. Ocular motor apraxia appears to involve a higher order of conjugate control of the eyes than in the case of the simple paralyses of conjugate gaze. It is more strictly limited to the sphere of volitional control."

SPAETH, Philadelphia.

TUMOR OF THE OPTIC DISK ASSOCIATED WITH NEUROFIBROMATOSIS. R. H. TRUEMAN and I. E. RUBIN, A. M. A. Arch. Ophth. **50**:468 (Oct.) 1953.

Tumors of the optic disk associated with neurofibromatosis are exceedingly rare. Prior to the presentation of this case only two other such cases have been reported in the literature. The authors compare their case with those previously presented, one in 1938 by Stallard, and the other in 1949, by Goldsmith. Perhaps the most interesting aspect of the present case was the fact that 15 years earlier the patient had had careful examinations at an eye clinic, with a recorded record of the examination at that time indicating the suspicion of some type of tumor of the optic nerve but making no diagnosis. In Stallard's case the patient had, in addition to the tumor of the optic nerve, an intracranial neuroma, responsible for death. Goldsmith's patient had a bilateral acoustic neuroma, and Trueman and Rubin's patient had a neurofibroma of the cervical region of the spinal cord.

SPAETH, Philadelphia.

OPTIC NEUROPATHY IN MULTIPLE SCLEROSIS. S. GARTNER, A. M. A. Arch. Ophth. **50**: 718 (Dec.) 1953.

Gartner reports a study of the neuropathy of 14 eyes obtained from 10 patients upon whom the diagnosis of multiple sclerosis was confirmed by autopsy findings. Each patient showed, before death, a defect either in the eye or in the optic nerve. The findings emphasized some facts connected with the eye and the optic nerve, not very commonly considered, such as, for instance, that "the optic nerve is not a nerve in the ordinary sense of the word. It is functionally and actually a tract in the central nervous system and is involved in multiple sclerosis along with other parts of the white matter of the central nervous system."

Any bundle of nerve fibers may be attacked by the plaque in the optic nerve. Involvement of the papillomacular bundle causes a dramatic loss of vision and draws the attention of the patient to the condition, so that a diagnosis is made in many cases. While the papillomacular bundle is frequently involved, the disease is by no means confined to it, as in the cases studied by Gartner. In addition, there is usually degeneration of nearby, also peripheral, fibers. In one case a large bundle of nerve fibers on the nasal side was atrophied.

"Many of the optic nerves showed very extensive damage, so that it was questionable whether it all occurred in one attack. The clinical descriptions of multiple sclerosis often point out that one attack of optic neuritis is the rule and recurrences are exceptional. The pathological evidence makes this questionable. Elsewhere in the central nervous system large numbers of plaques of different ages is a common finding, and there is no reason that the optic nerve should be an exception. The extensive atrophy of the optic nerve suggests repeated attacks in many cases. After the initial attack has left much damage in its wake, recurrences are likely to be unnoticed."

In general the important findings were optic nerve atrophy, partial usually, with extension of this to the nerve fiber layer and the ganglion cells, the atrophy being especially noted at the macula.

SPAETH, Philadelphia.

NASOPHARYNGEAL FIBROSARCOMA IN A CHILD EXTENDING INTO THE CEREBELLOPONTINE ANGLE. B. S. EPSTEIN, Am. J. Roentgenol. **71**:60 (Jan.) 1954.

Epstein reports a case of a nasopharyngeal tumor which presented with the symptoms of a brain tumor and without any symptoms to suggest involvement of the nasopharynx. The patient had no bleeding, no obstruction of breathing, and no evidence of enlarged cervical lymph nodes. The neurological symptoms progressed rapidly, and the patient died before exploration could be carried out. The first symptom was an appearance of displacement of the right eye inward. Within two weeks the right eye was closed, and the patient could not walk properly. He suffered a right facial weakness and could not speak properly. Hearing on the right side was lost. There was weakness of the left upper extremity associated with a fine tremor.

Plain roentgenograms of the skull showed no abnormality. A soft tissue shadow in the nasopharynx was interpreted as normal adenoid tissue. A ventriculogram showed evidence that suggested the presence of a mass in the pontine region on the right side. The clinical impression was that the child had a right posterior fossa tumor.

An autopsy showed that the child had a flat tumor of the posterior wall of the nasopharynx which had invaded the posterior fossa through the base of the skull, without involving the basilar foramens. The tumor was well encapsulated and did not invade the brain. It occupied the right cerebellopontine angle and extended across the midline, pushing the brain stem to the left. The histologic diagnosis was periosteal fibrosarcoma.

WEILAND, Grove City, Pa.

DEATH DUE TO WITHDRAWAL OF BARBITURATES. H. F. FRASER, M. R. SHAVER, E. S. MAXWELL, and H. ISBELL, Ann. Int. Med. **38**:1319 (June) 1953.

The authors describe the clinical and pathologic findings in a case in which death was apparently due to the severe stress of the barbiturate abstinence syndrome superimposed on an already damaged cardiovascular system. The occurrence of this death points up the opinion previously ventured by Isbell that abrupt withdrawal of barbiturates from chronically intoxicated persons is very dangerous and generally contraindicated. Withdrawal in this case was accidental and due to the patient's concealment of his enormous barbiturate intake from the physicians who were attempting to treat him. Had the diagnosis been made in time, proper treatment would have consisted of parenteral administration of barbiturates in sufficient quantity to induce 8 to 12 hours of unbroken sleep, followed by regular oral doses of amounts of barbiturates sufficient to maintain a definite, continuing moderate degree of intoxication. After several days on this regime, the dose of barbiturates should have been reduced cautiously (no more than 0.1 gm. daily) until withdrawal was complete.

A special study was made in this case, in a search for mucoid bodies or globules scattered throughout the white matter or in the nerve cells themselves. No such collections were seen, and there was no evidence of degeneration of the basal ganglia grossly, as is sometimes described in barbiturate intoxication.

ALPERS, Philadelphia.

VARIATIONS OF E. E. G. PATTERNS IN A CASE OF NEUROSYPHILIS. L. J. SEELEY and R. S. DILLE, Dis. Nerv. System **14**:138 (May) 1953.

A 35-year-old white man developed a primary syphilitic lesion in 1939 and received inadequate metallic therapy. In 1942, in the Army, he was found to have positive serologic reactions of the blood and spinal fluid but was given only a few more injections of heavy metals. In 1948, and again in 1949, he had atypical convulsions. On the latter occasion an electroencephalogram was normal. In 1949 the patient was treated with 9,000,000 units of penicillin. A year later he had another seizure, and a brain wave tracing showed paroxysmal slow rhythms in the anterior leads, originating in the left hemisphere. A second course of penicillin, 4,500,000 units, was administered. The serologic reactions of both blood and spinal fluid remained positive, and after 12 months he was given an additional 9,000,000 units of the antibiotic. An electroencephalographic study done two months subsequent to this third stage of therapy was without pathological activity, as was a fourth, done in three months. Other reports in the literature note marked improvement in the cortical dysrhythmia of neurosyphilis following penicillin treatment, but

the authors believe that this case is unique in its progression from electroencephalographic normality to abnormality and the final reversion to normality with persistent therapy. The exact nature of the accountable lesion is not known but is presumed to be a reversible cortical endarteritis.

BEATON, Tucson, Ariz.

DORMIN [METHAPYRILENE] POISONING: A CASE REPORT. G. D. NISWANDER, Dis. Nerv. System **14**:239 (Aug.) 1953.

A 42-year-old paranoid and depressed male patient took 36 capsules (900 mg.) of the antihistamine methapyrilene in a suicidal attempt. He had for a week previously been using up to 4 capsules daily as a hypnotic, because of inability to obtain barbiturates. When hospitalized, two hours after swallowing the overdose, he complained of dizziness, lethargy, restlessness, and dryness of the mouth. Examination revealed pulse rate of 110, marked flushing of exposed portions of the skin, and slight dilatation of the pupils. Gastric gavage and emetics recovered some partially dissolved capsules. Thirty minutes later the patient had an explosive outburst of panic, in which he was apparently reacting to visual and auditory hallucinations. In the next hour he went through four cycles of alternating drowsiness and active delirium. Four hours after admission the patient was able to speak rationally; in 12 hours he showed no neurological or psychological abnormalities. It is emphasized that the clinical picture was much like that of an acute atropine intoxication. Excessive amounts of other antihistamines have been reported to produce similar symptoms of central nervous system stimulation, even to the occurrence of convulsions, though the drugs as a class are considered to be central depressants. Methapyrilene is a potentially dangerous medication in the possession of suicidally inclined persons.

BEATON, Tucson, Ariz.

CEREBRAL EDEMA AND ITS RELATION TO BARBITURIC ACID POISONING. L. H. MOUSEL, J. A. M. A. **153**:459 (Oct. 3) 1953.

Mousel reviews some of the experimental and clinical studies on anoxia of the central nervous system. He reports Lucas' findings that the earliest change in the anoxic brain is an intracellular edema and that withdrawal of fluid from the brain by osmotic means is the principle underlying treatment of cerebral edema. This can best be done by the use of concentrated human serum.

The treatment of barbiturate intoxication has been fairly standardized, one or a combination of the analeptic drugs being employed, along with general supportive therapy. Mousel and Essex, in a previous study, found that the analeptics were not only useless but actually harmful in treatment of barbiturate overdose.

On the supposition that cerebral edema is probably responsible for the severe complications frequently seen in barbiturate poisoning, Mousel has formulated for these patients a therapeutic treatment with 25% salt-poor human serum albumin. Three such patients, successfully treated, are described. All were treated with analeptic drugs before the serum albumin was administered, and in each instance the analeptics failed to improve the patient's condition.

The recovery phase in all three patients was similar. Reflexes returned in 8, 17, and 23 hours, respectively, after serum albumin was given. All of the patients showed signs of voluntary activity and return of consciousness within a few hours after return of the deep reflexes. There were no maniacal tendencies, and restraints were not required. This behavior is in sharp contrast to that of many patients recovering from barbiturate poisoning when the usual therapeutic agents are used.

Mousel makes this report with the hope that the use of analeptics will be abandoned in the treatment of barbiturate intoxication. Treatment should be directed toward correcting the cerebral anoxia by eliminating cerebral edema through the use of salt-poor serum albumin or some other agent that will accomplish the same result by action of its high osmotic pressure in drawing the intracellular fluid back into the circulation. General supportive treatment, such as adequate oxygen and fluid therapy, is essential, and measures should be taken to lower body temperature in patients who have hyperthermia.

ALPERS, Philadelphia.

SEX AND AGE IN MYASTHENIA GRAVIS AS CRITICAL FACTORS IN INCIDENCE AND REMISSION. R. S. SCHWAB and C. C. LELAND, J. A. M. A. **153**:1270 (Dec. 5) 1953.

Some clinicians are skeptical that there is any relation at all between myasthenia and the thymus gland. There is still some question as to the precise value of thymectomy in myasthenia gravis. Since there has been reported a difference in response to the operation in females and in males, Schwab and Leland plotted the onset of the disease according to decades in the two sexes in a total group of 367 patients. This graph showed a significant and surprising difference between males and females. The disease developed in 62% of the 202 females before the age of 31. In contrast to this early beginning in the females, in the 167 males the onset occurred before the age of 30 in only 27%. For females the mode (21%) onset age was 21 to 25 years, whereas for males the mode (30%) onset age was 61 years and over.

A group of 78 patients (53 female and 25 male) who underwent thymectomy was analyzed and compared with a similar group who had not had surgery. The patients of all ages and both sexes who had thymomas demonstrable by either gross or microscopic examination derived no evident improvement in their myasthenia from the operation. Males received no evident benefit from the operation. Thymectomy appears to be contraindicated in males whose onset of the disease was after the age of 30.

In females without thymomas thymectomy appears definitely indicated. In this series the incidence of unquestionable improvement in all 53 females who were subjected to thymectomy was 63%, as opposed to 34% in the controls. The mortality rate, including operative deaths, was 15% for female thymectomy patients and 28% for their controls. More data indicate that the disease is twice as common in young females as in young males and twice as common in older males as in older females.

In this series 22% of the 78 patients subjected to thymectomy had thymomas. The incidence of thymomas in ordinary necropsies (in cases without myasthenia) is less than 0.1%. In Schwab and Leland's thymectomy cases, 60% of the patients who did not have thymomas had abnormal thymic tissue in the sense that there was hyperplasia or presence of germinal center formations. The authors feel that the relationship between myasthenia and the thymus gland is indisputable. In view of the poor results of thymectomy in patients with thymomas and in male patients regardless of pathology, they suggest the likelihood that the causal agent is not the thymus itself but another endocrine disturbance that may cause both the thymic abnormalities and the myasthenia.

ALPERS, Philadelphia.

NEUROPSYCHIATRIC ASPECTS OF ABNORMAL PORPHYRIN METABOLISM. E. G. OLMSTEAD, J. Nerv. & Ment. Dis. **117**:300 (April) 1953.

Olmstead reports the case of a 31-year-old man who had recurrent episodes of depression, tension, and irritability during periods of increased excretion of uroporphyrin. During these same periods his EEG became abnormal, with 4½ to 5 cps activity and random diphasic spikes. Both his mood and his EEG improved when the porphyria was in remission.

BERLIN, Mount Vernon, N. Y.

FOCAL CEREBRAL INJURY DUE TO TRICHINELLA SPIRALIS. R. W. HURD, J. Nerv. & Ment. Dis. **117**:526 (June) 1953.

Hurd reports the case of a 49-year-old man who developed bloody diarrhea six days after the ingestion of inadequately cooked pork. He then developed edema of the eyelids. On the 10th day after eating the pork he began to have weakness of the right arm and leg, and he showed progressive clouding of the sensorium and impaired memory. His rectal temperature was 102 F. X-rays of the skull and the spinal fluid were consistently normal. On the 19th day after ingestion of the pork it was noted that he had a 25% eosinophile count. There developed a progressively increasing titer of the complement fixation test for trichinosis up to 800. The patient had a residual hemiparesis one year later, but x-rays of the skull were normal.

BERLIN, Mount Vernon, N. Y.

HEMIPLEGIA AND SEIZURES: AN ELECTROENCEPHALOGRAPHIC CORRELATION. W. A. STEPHENSON and D. R. BECKA, J. Nerv. & Ment. Dis. **118**:250 (Sept.) 1953.

Electroencephalograms were obtained on 114 of a group of 291 patients with hemiplegia resulting from vascular lesions. In this group, 77.2% had abnormal EEG's. Of the 19 patients with normal waking EEG's, 7 showed abnormalities in amplitude asymmetry in sleep spindles. Eleven records showed generalized slow activity, but focal slowing was the commonest abnormality, and 55 cases showed a definite focus of slow-wave activity.

The occurrence of seizures was reported in 13.1% of the group of 291 cases. Generalized seizures occurred at an earlier age than did localized seizures. Of the group with seizures, 18 had abnormal records and 2 had normal waking records. There was no reliable EEG basis for differentiation between seizures and nonseizure cases. Only 9 of the 30 cases with seizures had frequent seizures, whereas the others had single or infrequent convulsive phenomena.

Seventy-five per cent of the subjects had EEG abnormalities more than one year after the onset of the hemiplegia, whereas 78.5% had abnormalities within less than one year after the onset of hemiplegia.

BERLIN, Mount Vernon, N. Y.

INCIDENCE OF APNEA AT BIRTH IN THE ENCEPHALOPATHIES OF CHILDREN. G. TARDIEU, M. R. KLEIN, J. P. HELD, and J. TRELAT, Rev. neurol. **89**:22, 1953.

Apnea at birth, occurring for at least 15 minutes, was used as the criterion for comparison of 629 children with cerebral defects with 280 control subjects. In the group with an I. Q. of less than 50, prolonged apnea was observed in 13.5%, but only 2.5% of the normal subjects had comparable apnea. Of 81 cases of infantile hemiplegia, 12% had apnea lasting more than 15 minutes, and 19% had apnea for less than 15 minutes. Among the patients with cerebral diplegia, 15% had apnea of more than 15 minutes.

BERLIN, Mount Vernon, N. Y.

PROGNOSIS FOR REVIVED NEWBORN INFANTS. G. TARDIEU and J. TRELAT, Rev. neurol. **89**:259, 1953.

Of a group of 166 infants, 35 required resuscitation for less than 15 minutes. In this group 22.8% showed defects of mentation. Of the infants apneic for more than 15 minutes, five had motility disturbances, and of those apneic for less than 15 minutes, four had motility disturbances. Only 39.5% of infants who were apneic more than 15 minutes failed to have disorders of motility. The authors conclude that disorders of intelligence, motility, and behavior are more frequent and more serious in infants who are apneic at birth, especially if the apnea is longer than 15 minutes.

BERLIN, Mount Vernon, N. Y.

Treatment, Neurosurgery

TREATMENT OF TUBERCULOUS MENINGITIS. W. W. WADDELL JR., A. P. BOOKER, W. C. GREGORY, and O. B. BOBBITT, A. M. A. Am. J. Dis. Child. **87**:273 (March) 1954.

The report presents the results of the treatment of two series of children with tuberculous meningitis. The first consisted of 19 patients treated with intramuscular and intrathecal streptomycin, oral paraaminosalicylic acid and/or thiazolsulfone (Promizole). The second series consisted of six patients treated more recently with the use of intramuscular streptomycin and oral paraaminosalicylic acid and isoniazid. In the first group only eight (42%) survived, of which only four were without mental or neurologic defects.

Although the second series was small, it was considered a striking contrast to the first group, because two-thirds are alive and in remarkably good condition. The longest follow-up, however, was one year at the time of writing. The remaining two patients, who did not survive, were in poor condition when admitted. The present regimen of treatment consists of intramuscular streptomycin, 40 mg. per kilogram of body weight per day until the clinical course and the cerebrospinal fluid are normal, and then three times weekly for a total course of at least six months; oral paraaminosalicylic acid, 0.3 gm. (average) per kilogram of body weight per day, in divided doses, for at least 12 months, and oral isoniazid, 5.0 mg. per kilogram of body weight per day, in divided doses, for at least 12 months.

In addition, data are presented on the determination of the serum and cerebrospinal fluid isoniazid levels, as well as on the detailed method of determination. Serum levels showed an average peak three or four hours after administration, while the cerebrospinal fluid levels reached their peak in four to six hours. The serum levels were higher than the cerebrospinal fluid levels in the patients with tuberculous meningitis. In one patient (control) with miliary tuberculosis there was no appreciable difference in these levels.

The authors believe that the present combination of the three drugs is logical, particularly in delaying the emergence of strains resistant both to streptomycin and to isoniazid. They do not believe intrathecal injections of irritating materials is an ideal form of therapy.

SIEKERT, Rochester, Minn.

TRICEPS SURAE SYNDROME IN CEREBRAL PALSY. L. D. BAKER, A. M. A. Arch. Surg. **68**:216 (Feb.) 1954.

In the past decade the conservative management of cerebral palsy has been favored and the benefits of surgical intervention minimized. Baker recommends wider use of surgical corrective procedures. In certain patients with spasticity of the lower extremities and equinus deformity of the feet, recession of the heads of the gastrocnemius will permit dorsiflexion of the ankle and extension of the knee, with the ankle dorsiflexed. Furthermore, the foot clonus will be reduced. This procedure should be considered before lengthening of the Achilles tendon is attempted or a partial neurectomy of the triceps surae is done.

LIST, Grand Rapids, Mich.

SURGICAL TREATMENT OF SYRINGOMYELIA. NICHOLAS WETZEL and LOYAL DAVIS, A. M. A. Arch. Surg. **68**:570 (April) 1954.

Twenty-eight patients with syringomyelia were treated by laminectomy. In two cases only an aspiration of the syringomyelitic cavity was done. In the remaining 26 cases, a longitudinal myelotomy was performed. There were two surgical deaths. Of the surviving 26 cases, 10 showed no further progression of the disease, and 7 showed postoperative improvement, which in some of the cases was maintained over a period of many years. The authors feel that patients with syringomyelia may be definitely benefited by myelotomy and drainage of the cord cavity.

LIST, Grand Rapids, Mich.

EPILEPTIC PATIENTS TREATED WITH AUREOMYCIN [CHLORTETRACYCLINE]: CLINICAL AND ELECTROENCEPHALOGRAPHIC CHANGES. F. W. STAMPS, E. L. GIBBS, and E. HAASE, Dis. Nerv. System **12**:227 (Aug.) 1951.

Twenty-five patients with severe epilepsy, uncontrollable by maximal doses of the usual drugs, were treated with chlortetracycline (Aureomycin). Seventeen were persons in whom postencephalitic convulsive disease was suspected. Dosage of the antibiotic consisted of 250 to 500 mg. for children and 500 to 750 mg. for adults, given four times a day, in addition to current antiepileptic medication. In small children chlortetracycline in these amounts could not be tolerated without reduction in the anticonvulsants. In 10 cases, the electroencephalogram showed a lessening of seizure activity; in 7, such activity largely disappeared. Clinical improvement paralleled the electroencephalographic clearing. Four patients became attack-free, even with decreased intake of antiepileptic substances. The only drugs previously known to have a normalizing effect on a paroxysmal electroencephalogram are trimethadione (Tridione) and paramethadione (Paradione), and their effect is confined to petit mal. Chlortetracycline seems to benefit a group of patients with a wide variety of dysrhythmias. Nine cases that showed improvement were postencephalitic, and one case of cerebral palsy was helped. No patient was bettered whose seizures were due to head trauma or who gave no history of associated febrile illness. Children who had behavior disorders in addition to epilepsy were reported by parents as less unstable after treatment with chlortetracycline was begun. It is concluded that the antibiotic probably blocks a chronic encephalitic process which causes the attacks, but that a metabolic effect on cerebral neurons cannot be ruled out.

BEATON, Tucson, Ariz.

COURSE AND MANAGEMENT OF MYASTHENIA GRAVIS. D. GROB, J. A. M. A. **153**:529 (Oct. 10) 1953.

A total of 202 patients with generalized myasthenia gravis were studied in the Johns Hopkins Hospital for 1 to 34 (average 8) years. Of these, 32% died within an average of six years after onset, 13% are in a complete or nearly complete remission, 25% have improved to a moderate degree, 20% are unchanged, and 10% have become worse. One-fourth of the patients have had complete or nearly complete remission of their disease at some time during its course, the average length of remission being 4.6 years.

The course of 44 patients who were subjected to thymectomy and of 40 patients who had irradiation of the thymus was, in general, only slightly better than the course of 118 patients who had neither procedure. Fifteen patients had a thymoma. Ten of these patients had a rapid, fulminating course, terminating in death, regardless of whether thymectomy was performed.

When localized ocular myasthenia gravis became generalized, it usually did so within the first year of the disease. The majority of patients who had localized ocular myasthenia for more than one year did not have further extension of the disease during a period of observation of 1 to 41 (average 8½) years. The maximum strength attainable with tetraethylpyrophosphate (TEPP), octamethylpyrophosphoramide (OMPA), or neostigmine bromide, or with their combination, was approximately the same, but TEPP or OMPA provided somewhat more sustained strength and better endurance than did neostigmine bromide in most patients.

Grob points out that the most promising lines of further investigation seem to be the study of the relation of myasthenia gravis to the glands of internal secretion and the study of the underlying defect in neuromuscular function.

ALPERS, Philadelphia.

ANTISPASMODIC COMPOUND 08958 [CYCRIMINE HYDROCHLORIDE] IN TREATMENT OF PARALYSIS AGITANS. K. R. MAGEE and R. N. DEJONG, J. A. M. A. **153**:715 (Oct. 24) 1953.

Perhaps the most significant observations to be made in the clinical study of paralysis agitans is that each patient's care must be strictly individualized. Many drugs have been introduced in the treatment of paralysis agitans with early enthusiasm, only later to be proved of little or no value.

In this study Magee and DeJong describe the work done on a series of 61 patients with paralysis agitans who received a therapeutic trial with the antispasmodic cycrimine hydrochloride (Compound 08958; 1-phenyl-1-cyclopentyl-3-[1-piperidyl]-1-propanol hydrochloride), since released by Eli Lilly & Company under the trade name Pagitane hydrochloride.

The majority of patients in the series had taken either scopolamine or trihexyphenidyl or both, and the effectiveness of these compounds, and other drugs, was noted and compared. Several other experimental drugs were used either before or after treatment with cycrimine. If the patient reported best results with cycrimine after failure with the other experimental preparations, he again received it for prolonged trial.

Of this group of patients, 46% received beneficial results superior to those obtained by standard medication. Side-effects were similar to those produced by other atropine derivatives. Careful adjustment of dosage was necessary to minimize these side-reactions.

The best results were obtained in the postencephalitic group, as is usually true with atropine derivatives. This may be due to the fact that these patients could tolerate much larger amounts of medication. On the other hand, those with idiopathic and arteriosclerotic conditions could not tolerate the medication nearly as well. Of particular interest were patients who received remarkable relief from oculogyric crises.

Six other patients who did not have paralysis agitans were given cycrimine. Of these, only one patient with dystonic movements of his upper extremities obtained good results.

The authors conclude that these preliminary studies have demonstrated that cycrimine has been of value in a limited series of patients with paralysis agitans and that it should be studied further in order to ascertain its definitive place in the treatment of this disorder.

ALPERS, Philadelphia.

Is Stellate Ganglion Block of Value in Stroke? J. E. Ruben and R. A. Mayer, J. A. M. A. **153**:1002 (Nov. 14) 1953.

Ruben has previously reported 100 cases of stroke treated by stellate ganglion block in which he felt the results favored the treated cases. This paper reports 58 previously unreported cases of stroke treated to maximum benefit with stellate ganglion block, in addition to usual routine management.

More than 60% of the patients showed some improvement immediately after the appearance of Horner's syndrome. In almost 70% of those showing improvement the benefit was striking. Since these were all private patients, their general medical and nursing care was probably above average and may account for the better-than-average results.

In this series, among the 43 acute apoplexy patients, cerebral thrombosis was both the commonest and the most responsive of the causes of cerebrovascular accident. Patients with encephalomalacia respond very poorly to stellate ganglion block or any other therapy, as shown by the results in six cases. Of the 17 with thrombosis, 11 had dramatic improvement; of the 4 with embolus, 2 had dramatic results, and of those with spasm, all had dramatic results.

On the basis of their experience and results, Ruben and Mayer believe that the possible benefits from stellate ganglion block should not be denied patients suffering from stroke due to embolism, thrombosis, or spasm.

Alpers, Philadelphia.

Treatment of Bell's Palsy with Cortisone. W. P. Robison and B. F. Moss, J. A. M. A. **154**:142 (Jan. 9) 1954.

Most authorities feel that in patients suffering with severe Bell's palsy recovery is not likely to occur in less than several months. Robison and Moss treated two patients with cortisone, and prompt recovery occurred.

With one, a girl aged 13, treatment was started on the third day of paralysis. Three days after the cortisone therapy was begun the patient showed improvement that was obvious and gratifying. During this time 400 mg. of cortisone had been given. For the next 10 days 75 mg. of cortisone was given each day (a total dose of 1,150 mg.), with continuing improvement. Recovery was complete 19 days after onset.

Cortisone therapy was started one week after onset of the paralysis in the second patient, a child aged 5 years. Cortisone was given in diminishing doses, and recovery was complete on the 17th day.

According to Rothendler, "the beneficial action of cortisone in these patients can be assumed to be due to a reduction of congestion and related ischemia of the nerve and its sheath in the bony canal." The authors suggest the use of cortisone in the early stages of Bell's palsy.

Alpers, Philadelphia.

Thymectomy in the Treatment of Myasthenia Gravis. R. T. Ross, Lancet **1**:785 (April 19) 1952.

Ross reports on the results of surgical removal of benign hyperplastic thymuses in 100 consecutive patients with myasthenia gravis. Eighty-seven per cent showed complete relief of symptoms, considerable or moderate improvement, or improvement as judged by the reduction in daily neostigmine requirements after operation. The average period of follow-up after operation was four and one-half years. The benefit from surgery was greatest in those patients in whom the myasthenia was of shortest duration. In this series the age of the patient at the onset of his illness was not significant. A comparison with three large series of patients treated by medical means alone revealed that the proportion of cured or greatly improved patients was smaller in the latter group and the proportion of deaths due to myasthenia gravis was much higher.

Madow, Philadelphia.

Encephalography, Ventriculography and Roentgenography

PNEUMOENCEPHALOGRAPHY IN CHILDREN WITH MENTAL DEFECT AND/OR CEREBRAL PALSY. N. MALAMUD and B. GAROUTTE, A. M. A. Am. J. Dis. Child. **87**:16 (Jan.) 1954.

Malamud and Garoutte studied the brains of 30 feeble-minded patients and correlated their findings with pneumoencephalograms obtained during life. There were 20 cases with malformations ("primary" amentias). Of these, 17 showed various nonspecific cerebral anomalies with disturbance of the pattern of the gyri and sulci. The majority had small frontal and occipital lobes. Ventricular enlargement, laking of gas in the frontal area, and flattening of the occipital bone were observed. Three cases presented agyria. In these, marked hydrocephalus was present; only a small amount of air was seen over the smooth convexity, and it lacked the normal linear collections.

Ten cases comprised the destructive cerebral lesions ("secondary" amentias). A history of birth trauma or postnatal infection of the central nervous system was usually obtained. These cases showed ventricular enlargement (unilateral in cerebral hemiatrophy) and often absence of air over the convexities. In cerebellar atrophy enlargement of the fourth ventricle was observed more commonly than an enlarged cisterna magna.

SIEKERT, Rochester, Minn.

MYELOGRAPHIC DEMONSTRATION OF CYSTS OF SPINAL MEMBRANES. L. G. JACOBS, J. K. SMITH, and P. S. VAN HORN, Radiology **62**:215 (Feb.) 1954.

Jacobs and associates report the case histories of two patients who had cysts which lay adjacent to the spinal canal and were filled with fluid because of their communication with the subarachnoid space. In each of the two cases a myelogram was obtained and the cysts retained the opaque material.

One patient had an extradural meningeal cyst lying behind the subarachnoid space at the level of the ninth thoracic vertebra. Extradural meningeal cysts apparently arise by distention of the meninges at a point of congenital weakness near the exit of a nerve root. These cysts produce symptoms and signs which suggest cord tumor or herniated intervertebral disc. Often the symptoms show remissions if the cyst ruptures or drains through a communication with the subarachnoid space. The symptoms return when the cyst distends again. A history of remission of symptoms may lead the unwary to make a diagnosis of multiple sclerosis. The cyst may present no specific x-ray changes. Widening of the spinal canal or erosion of pedicles at the level of the cyst is sometimes seen. Myelograms usually demonstrate a partial or complete block at the level of the cyst. However, it is exceptional for the opaque medium to enter the cyst, since communication with the subarachnoid space is usually lost in the evolution of the cyst. The case which Jacobs and associates describe is the first one to be reported in which the cyst was filled with the opaque medium.

The second patient had a perineurial cyst. These cysts arise from a dehiscence in the connective tissue sheaths lining the nerve roots in the sacral region of the spine. The symptoms they produce are indistinguishable clinically from symptoms of a herniated intervertebral disc. Myelography is usually helpful to demonstrate that there is no evidence of a herniated intervertebral disc. In the case reported by Jacobs and his associates some of the opaque medium used in the myelogram entered several small perineurial sacral cysts and became trapped there. Both the perineurial cysts and the extradural meningeal cyst were found at the operation which followed the myelographic study in each case.

WEILAND, Grove City, Pa.

Peripheral and Cranial Nerves

BILATERAL OPTIC NEURITIS FOLLOWING SMALLPOX VACCINATION AND DIPHTHERIA-TETANUS TOXOID. W. U. MCREYNOLDS, W. H. HAVENER, and M. A. PETROHELOS, A. M. A. Am. J. Dis. Child. **86**:601 (Nov.) 1953.

A 7-year-old girl had sudden onset of decreased visual acuity 11 days after she received a booster dose of diphtheria and tetanus toxoid alum-precipitated U.S.P. and a smallpox vaccination. The entire upper arm had been markedly swollen for several days after this injection. She had received a series of diphtheria-pertussis-tetanus inoculations at 6 months of age and also a smallpox vaccination, which was unsuccessful.

Examination three days after the onset of the visual trouble disclosed a visual acuity of 6/100 in the right eye, not improvable by lenses. There was no light perception in the left eye. The discs were hyperemic with blurred margins. Visual field of the right eye disclosed a central scotoma and generalized peripheral constriction. General physical examination and the remainder of the neurologic examination were normal. The cerebrospinal fluid contained 3 to 4 cells per cubic millimeter. Laboratory studies were otherwise normal.

Treatment with corticotropin and mannitol hexanitrate was given. The visual acuity and fields showed prompt and progressive improvement. Two and one-half weeks after onset the fundi were normal except for slight blurring of the left disc. Visual acuity was then 6/9 in the right eye and equal to finger counting in the left eye at 2 ft. (60 cm.). The visual field of the right eye was normal; the left contained a central scotoma. Two months after onset the visual acuity was 6/6 — 3 bilaterally; the discs showed no pallor.

SIEKERT, Rochester, Minn.

VISUAL FIELD CHANGES IN OPTIC NEURITIS. M. CHAMLIN, A. M. A. Arch. Ophth. **50**: 699 (Dec.) 1953.

Chamlin studied 100 cases of optic neuritis, both papillitis and retrobulbar neuritis, and reports the field changes found in these cases. No brain tumor cases were used, and no cases were utilized in which there was any reasonable doubt as to the correctness of the diagnosis. The cecocentral scotoma, with a relatively intact periphery, was found in 52% of the cases and probably occurs with equal frequency in papillitis and in retrobulbar neuritis. The periphery was involved in 24% of the cases. In only one case was an isolated peripheral defect found which had no connection with the area caeca, and this case may possibly be considered one of periaxial neuritis. In cases of paracentral and peripheral involvement of the field, the area most frequently involved was the lower field, particularly the lower nasal field. The fixation point, and therefore central visual acuity, was spared in 37% of the cases. Of these 37 cases, 21 were seen at the onset of the disease; one, therefore, may safely say that certainly in at least 21% of the cases of optic neuritis central visual acuity is maintained. This is corroborative evidence that the preservation of central visual acuity alone must not be used as a major criterion for differentiating optic neuritis from other conditions, such as papilledema.

The various defects were subdivided into five classes: Group 1, cecocentral defects (52 cases); Group 2, paracentral nerve fiber bundle defects (24 cases); Group 3, paracentral nerve fiber bundle defects reaching to the periphery (9 cases); Group 4, nerve fiber bundle defects involving fixation and periphery (11 cases), and Group 5, peripheral defects only (4 cases).

It was interesting that central field involvement was present as often in cases of frank papillitis as in cases of retrobulbar neuritis. This is certainly a case against using the term "retrobulbar neuritis" to denote central scotoma, since papillitis is not unlikely to produce a central scotoma as well. Chamlin states, "It would, therefore, be rather difficult for me to believe that there is a sharp anatomical delineation between pure papillitis and pure retrobulbar neuritis, and that true papillitis is more apt to cause defects that spare fixation."

SPAETH, Philadelphia.

TOURNIQUET PARALYSIS SYNDROME. J. MOLDAVER, A. M. A. Arch. Surg. **68**:136 (Feb.) 1954.

Application of a tourniquet to an extremity may produce motor and sensory paralysis. This is the result of a local mechanical pressure rather than of ischemia. The clinical syndrome is characterized by the following signs and symptoms:

The site of the lesion may be indicated by a cutaneous line of pigmentation. There is paralysis with hypotonicity but without gross muscular atrophy. As a rule, the sensations of touch and vibration and the position sense are completely abolished, but the sensations of pain and temperature are affected only slightly. Frequently there is an actual hyperalgesia with a lower pain threshold; in severe cases, pain sensation is delayed, owing to selective damage of the fast-conducting pain fibers. Subjective paresthesias are not experienced, nor can the Tinel sign be elicited because the conduction of tactile fibers is interrupted by the local lesion. Vegetative functions, such as sweating, pilomotor responses and vasomotor reactions, remain normal. Electrical examination reveals the presence of a localized block of nerve conduction; stimulation

distal to the lesion effects normal motor responses but no subjective tingling. Proximal stimulation causes tingling but elicits no muscular contraction. Thus, the site of the lesion can be determined by the electrical examination.

Return of function occurs in the following order: First, pain and temperature sensations come back; then position sense, vibratory sensation, and motor function, and, finally, tactile sensation. Two illustrative cases are reported in detail.

LIST, Grand Rapids, Mich.

Congenital Anomalies

ARACHNODACTYLY ASSOCIATED WITH ANEURYSM OF THE AORTA. H. S. TRAISMAN and F. R. JOHNSON, A. M. A. Am. J. Dis. Child. **87**:156 (Feb.) 1954.

Traisman and Johnson report two cases with autopsy, ages 9 months and 10 years, respectively, exemplifying the typical findings of Marfan's syndrome with an associated aortic aneurysm. Beside the characteristic arachnodactyly, muscular atrophy and, often, ocular and cardiac anomalies are seen. The 9-month-old infant appears to be the first infant to die of this disease.

SIEKERT, Rochester, Minn.

A FAMILIAL DYSTROPHY. J. HOZAY, Rev. neurol. **89**:245, 1953.

The report concerns two siblings who were offspring of a consanguineous marriage. The characteristics of this maldevelopment were that although the patients were normal at birth, at 3 years of age an arrest of growth of all four extremities occurred. The large toes were relatively small in proportion to the rest of the foot. Later, there developed a reduction in the size of the distal two-thirds of the extremities. The bony structures were disproportionately smaller than the soft tissues, with consequent folding over of the skin. Trophic disturbances of the skin appeared in the form of ulcerations and keratoses. There was no alteration in sensation, such as one might expect in syringomyelia. The facial maldevelopment consisted of a larger-than-normal biparietal and bizygomatic diameter, micrognathia, and infantile dental development. One of the siblings was mentally defective, but the other was normal. There were numerous freckles over the face and extremities.

BERLIN, Mount Vernon, N. Y.

News and Comment

STAFF REORGANIZATION, MONTREAL NEUROLOGICAL INSTITUTE

The Montreal Neurological Institute of McGill University has announced the following staff reorganization:

Dr. Theodore Rasmussen, recently Professor of Neurological Surgery at the University of Chicago, has joined the staff as Neurosurgeon and Professor of Neurology and Neurosurgery to undertake supervision of teaching and research.

Dr. Wilder Penfield continues as Director of the Institute and Chairman of the Department of Neurology and Neurosurgery in the Faculty of Medicine of McGill University.

The Institute laboratories will continue to be directed as follows:

Dr. William Cone, Surgical Neuropathology

Dr. K. A. C. Elliott, Neurochemistry

Dr. Herbert Jasper, Neurophysiology

Dr. Francis McNaughton and Dr. George Olszewski, Neuroanatomy and Medical Neuropathology

Direction of the clinical departments is as follows:

Dr. William Cone, Neurosurgeon-in-Chief and Professor of Neurosurgery

Dr. Francis McNaughton, Neurologist-in-Chief and Associate Professor of Neurology

Dr. Arthur Elvidge, Associate Neurosurgeon and Assistant Professor of Neurosurgery

Dr. J. Preston Robb, Assistant Director (Hospitalization) and Assistant Professor of Neurology

Dr. Herbert Jasper, Electroencephalographer and Professor of Experimental Neurology

Dr. Donald McRae, Neuroradiologist and Assistant Professor of Neurological Radiology

The Laboratory for Research in Multiple Sclerosis, started by Dr. Roy Swank, will be continued under the direction of Dr. J. B. R. Cosgrove.

NATIONAL MUSCULAR DYSTROPHY RESEARCH FOUNDATION, INC.

F. R. C. Brown, of Houston, Texas, who heads Texas Gulf Sulphur Company's land department, last week was named president of the National Muscular Dystrophy Research Foundation, Inc., only national charitable health organization chartered by the state of Texas, it is announced by Lloyd Gregory, of Houston, chairman of the board.

Mr. Brown has appointed Alf Roark, Houston attorney, and Charles W. Fisher, Jr., Liberty attorney and estate manager, to the executive committee. J. C. Smyth, editor-manager of *The Liberty Vindicator*, is a newly elected director.

A fund-raising and educational campaign, planned by the directors, includes "Coffee Day" and the annual national "Prayer Crusade," which are among successful drives conducted previously by the Foundation.

An additional grant of $1,500 from the research fund to the Southwest Foundation for Research and Education at San Antonio is announced. The muscular dystrophy group has previously made grants totaling $5,000 to the San Antonio foundation toward a $30,000 medical research project entitled "Individual Metabolic Patterns for Members of Families Having a History of Muscular Dystrophy." The project is conducted by Dr. Roy B. Mefferd, Jr., Associate Research Biochemist, under the supervision of Dr. N. T. Werthessen, Director of the Biological Division.

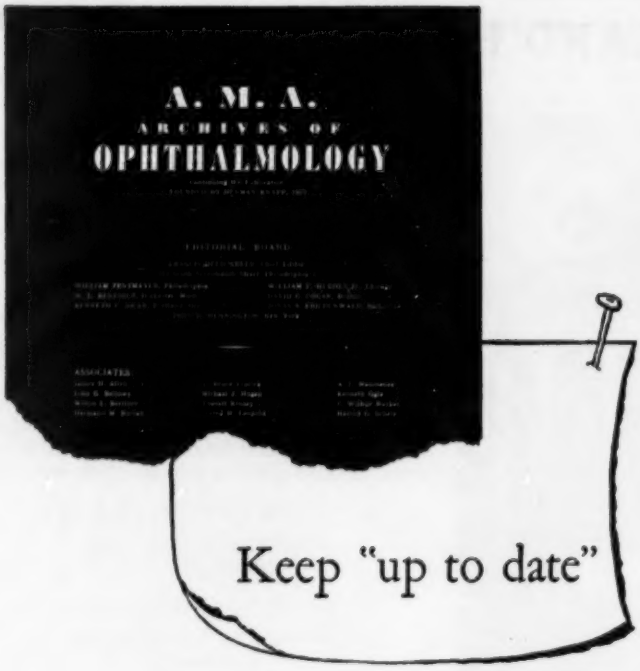
The Foundation's Medical Advisory Board is headed by Dr. Henry R. Viets, noted Boston neurologist. Dr. D. Denny-Brown, James Jackson Putnam Professor of Neurology at Harvard Medical School, is Research Advisory Board Chairman.

The nation's original muscular dystrophy group, whose abbreviation is NMDRF, was founded in 1950 by two Liberty sisters, Sallie and Nadine Woods, who are victims of the disabling disease. Mrs. Dwight D. Eisenhower is Honorary Foundation President. Sponsors are Price Daniel, junior United States senator from Texas, Governor Allan Shivers, and Mr. and Mrs. Roy Rogers, of screen, radio, and TV fame.

PERCIVAL BAILEY TO ADDRESS THE NEW YORK SOCIETY OF NEUROSURGERY

Dr. Percival Bailey, Professor of Neurology and Neurological Surgery, University of Illinois, Chicago, will deliver the 1954 Charles A. Elsberg Lecture, established by the New York Society of Neurosurgery, on Tuesday, Nov. 16, 1954, at 8:30 p. m., at the New York Academy of Medicine, 2 E. 103d St., New York. Dr. Bailey has chosen as his subject "Psychomotor Epilepsy—Its Relation to the Visceral Brain."

Preceding the lecture, a dinner in Dr. Bailey's honor will be held in the President's Gallery of the New York Academy of Medicine.



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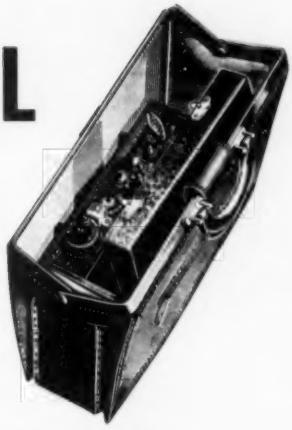

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